Comparison of the alanine response to clinical proton and carbon ion beams

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Purposes: Hadrontherapy with proton and carbon ion scanning beams is an advanced radiation treatment modality mainly exploiting the finite range of those particles in the matter, to better spare critical organs close to the tumor volume as compared to photons. However, the complexity of this treatment technique requires careful management of dosimetric uncertainties to guarantee patient safety. This study aims to reassess the suitability of alanine-based dosimetry for modern hadrontherapy applications and compare its dosimetric behavior with that observed under photon irradiation.

Materials and methods: Alanine pellets based on electron spin resonance (ESR) were used as passive dosimeters. The response was taken from the peak-to-peak amplitude of the main radiation-induced signal and correlated to the dose measured using an ionization chamber. The dosimetric characterization of alanine detectors was assessed in terms of the linearity of the response and dependence on energy, beam direction, and linear energy transfer (LET), for both pristine Bragg peaks and spread-out Bragg peak (SOBP) conditions. Photon irradiations were performed with a 6 MV linear accelerator at the San Matteo Hospital, while with charged particles at CNAO, both located in Pavia, Italy.

Results: Alanine showed a linear dose-response for both protons and carbon ions in the range of 10-50 Gy. LET effects reduced the alanine effectiveness by up to 30%. This quenching effect was more pronounced in the Bragg peak region and for carbon ions. Energy dependence was only observed for carbon ion beams.

Conclusions: Alanine is a reliable and promising dosimeter for use in the field of hadrontherapy. However, LET and energy dependence effects need to be taken into account.

Keywords: alanine; carbon ion beams; dosimetry; ESR; protons; quenching.

Introduction

Alanine is a type of amino acid, which refers to 2-aminopropanoic acid, and is distinguished by the presence of the methyl group. Depending on the configuration, it can be found in its D and L-alanine forms and a mixture of both. The latter two are the most used in the field of dosimetry (Baffa and Kinoshita 2014). The interaction with ionizing radiation induces the production of radicals (which are paramagnetic centers) in the material. As the concentration of these radicals is proportional to the radiation dose and can be measured via electron spin resonance (ESR), the technique can therefore be used for dosimetry purposes (Regulla and Deffner 1982).

The use of alanine has been widely spread due to its excellent dosimetric characteristics, including a linear response for a large range of doses (from around 2 Gy up to 10^5 Gy); the effective atomic number value close to the water one, meaning tissue-equivalence; a non-destructive reading process, that allows for reading irradiated samples many times; independence on the dose rate for absorbed doses within clinical use; low level of uncertainty (lower than 1% for doses above 5 Gy); among other aspects (Regulla and Deffner 1982; Onori et al. 1997; Sharpe and Sephton 1998; Anton 2006; Desrosiers et al. 2008; Desrosiers and Puhl 2009; Baffa and Kinoshita 2014). Additionally, the material proved to be sensitive to different radiation types, such as photons, protons, neutrons, and ion beams (Onori et al. 1997; Marrale et al. 2007; Baffa and Kinoshita 2014; Marrale et al. 2016).

Alanine as a radiation detector has been proposed since the 1960s (Bradshaw et al. 1962), and its versatility has been kept up with the development of new modalities in irradiation delivery and radiotherapies. The application for photon and electron beams happened as early as the 1980s (Chu et al. 1989; Schaeken et al. 1996), until its establishment as a secondary dosimeter (Anton et al. 2008). Later, with the introduction and increase of use of proton beams, which allow for a different depth dose profile and are characterized by the Bragg peak condition, alanine has also shown to be a reliable option for dosimetry. It showed a linear dose response, low uncertainty, and excellent agreement with other detectors, such as ionization chambers (Onori et al. 1997; Marrale et al. 2016). Similar results have been found when carbon ion beams were used (Herrmann et al. 2011).

More recently though, the increase in complexity of treatment planning and delivery techniques poses a further challenge. Doses can be delivered in highly conformal and precise manners, and high-dose deposition with a steep dose gradient can be achieved even in small volumes. These conditions have hampered the use of some conventional and already established detectors, for example, due to the use of small fields, which can lead to unbalance in charge equilibrium and strong dependence on the detector size (Höfel et al. 2023). Among the modalities, volumetric modulated arc therapy (VMAT), in which single or continuous beam angles can be used around the patient in an arc-oriented trajectory to deliver the dose, has been recently investigated (Powers et al. 2024). Another breakthrough has been the use of ultra-high dose rates (UHDR), typically above 40 Gy/s, to promote the so-called FLASH effect. This effect has been attributed to a wider treatment window and, consequently, a better sparing of healthy tissues, although the underlying mechanisms have not been elucidated yet (Favaudon et al. 2014; Tang et al. 2024). In the latter case, the extremely high dose rate can lead to saturation in typical active detectors, such as ionization chambers (Di Martino et al. 2022). First reports have shown that alanine is also effective for UHDR beams and can be used as a reference technique (Jorge et al. 2019; Romano et al. 2023).

Apart from the therapeutical approach, an aspect that has been a focus of attention over the decades is the effect of linear energy transfer (LET) on the response of alanine.

The use of low-LET radiation was first used in a broad scope in dosimetry, and in this case, the alanine response is more straightforwardly related to the absorbed dose. However, when high-LET radiation is used, the distribution of the dose throughout the path is not homogenous, which can lead to misestimation of the dose due to recombination processes of free radicals highly concentrated inside the particle tracks. Although differences in LET do not change considerably the shape of the ESR signal, that is, the same radicals are induced by different radiation qualities, there are differences in signal intensity. Hence, factors for radiation sensitivity are taken into account, such as the relative effectiveness, or RE (Hansen and Olsen 1985; Fattibene et al. 2002). In the case of proton irradiation, alanine has been already tested with therapeutical beams and showed good agreement with other detectors (Gall et al. 1996). Samples inserted into phantoms were used to evaluate the dose in Bragg peak and spread-out Bragg peak (SOBP) conditions. Results from ESR alanine were compared to ionization chamber ones (calibrated via ^{60}Co source), and absolute variations were within 2% (Onori et al. 1997). This agreement has been also found even when different techniques of beam delivery were employed (Marrale et al. 2016; Carlino et al. 2018; Palmans et al. 2018).

In terms of ion beams, there has been an interest in using alanine to investigate its application on mixed particle fields, which are common in particle therapy (Herrmann et al. 2011), but also to identify and estimate LET effects on its ESR signal (Michalec et al. 2024).

In this regard, this study aimed to investigate the response of alanine to different radiation qualities, in a therapeutical scope, and more specifically, in hadrontherapy. The response is evaluated in terms of dose-response, energy, and angular dependence, as well as the dose distribution profile due to the Bragg peak and SOBP. The ESR signals obtained are converted into absorbed doses with a photon-based calibration curve. Results are compared to the ionization chamber, in order to observe possible, LET effects. The findings reported here corroborate the ones in the literature and are important for further potential implementation of alanine dosimeters in hadrontherapy with the required accuracy level.

Methodology

Alanine pellets

The alanine-based pellets used for the ESR measurements were produced by Harwell Dosimeters (STERIS Applied Sterilization Technologies, United Kingdom). The pellets have cylindrical conformation, dimensions of 4.8 ± 0.1 mm, height of 2.8 ± 0.1 mm, and mass of 60 ± 2 mg.

ESR spectroscopy

The ESR radiation-induced signal of alanine was measured with a Bruker ELEXSYS spectrometer, model E580 (Bruker, Germany). This equipment has a cylindrical cavity and operates in the X band (microwave frequency of approximately 9.80 GHz). The experimental setup included a sweep width of 3 mT, a modulation amplitude of 1 mT, and a sweep time of 50 s. Measurements were carried out at room temperature (25 ± 1 °C).

To deal with potential anisotropic effects on the ESR signal, the same measurement was performed four times for each pellet, changing its orientation inside the cavity. The ESR signal obtained was evaluated in terms of the peak-to-peak amplitude (or H_{pp}) of the principal line. The signal was normalized by the mass. For each irradiation dose, up to 4 pellets were used to obtain a reproducible value (Marrale et al. 2016). The results are given in terms of average and standard deviation for the set of measurements for the same dose.

Ionization chamber

As a ground reference for dose estimation, measurements with calibrated ionization chambers were carried out in parallel with the alanine pellets. The absorbed dose to water was determined according to the recommendations given in the IAEA Technical Report No. 398 (Rev. 1) (IAEA 2024). An Advanced Markus Chamber, model 34045 (PTW-Freiburg, Germany), with a sensitive volume of 0.02 cm^3, was used for protons and carbon ion beams, while a 0.6 cm^3 sensitive volume Farmer ionization chamber, model 30013 (PTW-Freiburg, Germany), was used for photons.

Irradiation procedures

Proton and carbon ion irradiations of the alanine samples were carried out at the National Center for Oncological Hadrontherapy (CNAO), in Pavia, Italy, using the CNAO synchrotron and pencil beam scanning (PBS) dose delivery modality. Beam energies can range from 62 up to approximately 230 MeV for protons, while between 115 and 400 MeV/u in the case of carbon ions. These values correspond to Bragg peak depths in water ranging from 30 to 320 mm and from 30 to 270 mm, for protons and carbon ions, respectively (Mirandola et al. 2015). For photons, the irradiations were performed using the 6 MV Versa HD^{TM} linear accelerator (Elekta, UK) available at the San Matteo Hospital, also in Pavia.

Phantoms and detectors setup

In the irradiation procedure, alanine pellets were inserted into either water or water-equivalent medium, to simulate the conditions of attenuation and scattering in the human body. For the equivalent material, RW3 phantom slabs (PTW Freiburg GmbH, Germany) with dimensions of 30 cm × 30 cm each and varying thicknesses were used. For dose-response and energy dependence analyses with photons, the pellets were put into the slabs at a depth of 10 cm, while for angular dependence, at 14 cm deep for 0° and 90° for planar configuration (Figures 1A and B), and 16 cm deep for 0° (repeated for reference), 30° and 60°, for cylindrical one (Figures 1C and D). For proton and carbon ion beams, the alanine pellets were inserted at 18 mm deep (dose-response and energy dependence) into the RW3 slabs. All the depths are measured from the surface of the topmost slab to the center (not the surface) of the alanine pellet that was irradiated.

To investigate the quenching effect, due to response dependence on LET, both a pristine Bragg peak and an SOBP were used (ICRU 2016). In the case of proton irradiation in a Bragg peak condition, pellets were irradiated at 20, 130, 140, and 151 mm in a water phantom, inside a waterproof custom holder. For SOBP in both proton and carbon ion beams, pellets were also allocated in water at depths of 125, 150, and around 175 mm (proximal, middle, and distal portion of the SOBP, respectively). The dose-averaged LET values at those depths were 3, 3.5, and 5 keV/μm for protons and 35, 45, and 100 keV/μm for carbon ions, respectively. No irradiation was performed along the pristine Bragg peak for carbon ion beams, the thickness of the pellets being too large compared to the width of the Bragg peak itself. That is, the volume averaging effect on alanine dose response would have been too high to give reasonable results.

Conventional therapy: photons

Irradiation with photons was performed using a beam energy of 6MV, irradiating an area of 10 × 10 cm^2, with the beam perpendicular to the pellets. Both flattening filter-free (FFF) and flattening filter (FF) conditions were used, in the first case each pellet was irradiated individually, while in the former case, all 4 pellets could be irradiated together due to the uniformity of the field. The response of ESR alanine was evaluated for doses from 5 up to 40 Gy. For assessing the angular dependence, the radiation incidence angle was varied from normal to 30 and 60° to observe any differences in signal. A semi-cylindrical phantom was used to have the same attenuation effects in all directions (see Figures 1C and D). Using only flat slabs, the response was evaluated with an incidence at 0 and 90 °C (see Figures 1A and B).

Hadrontherapy: protons and carbon ion beams

ESR alanine signal response was evaluated for proton beam irradiation doses between 5 and 45 Gy. To investigate the linearity of the dose response, a beam energy of 148.8 MeV was used and the number of protons varied from $0.5 \cdot 10^9$ up to $4 \cdot 10^9$. The ESR signal was also evaluated as a function of the energy of the beam, for values of 81.6, 148.8, and 220.1 MeV, at a fixed number of particles (10^9). Angular dependence was investigated for radiation incidence angles of 30, 60, and 90°, for the 148.8 MeV beam energy. The depth dose distribution profile was analyzed for a Bragg peak curve (148.8 MeV beam energy) with the same experimental setup as for the dose-response analysis. A flat 6-cm thick SOBP was obtained using multiple beams with energies between 130 and 165 MeV (120-180 mm depth in water).

For carbon ion beams, the dose response of alanine was also analyzed up to 40 Gy, with a beam energy of 280 MeV/u, and by varying the number of ions from $20 \cdot 10^6$ up to $80 \cdot 10^6$. The energy dependence was studied for energy values of 150.7, 280, and 398.8 MeV/u, at a fixed number of particles ($20 \cdot 10^6$). For depth-dose profile analysis, an SOBP condition with a flat dose region between 120 and 180 mm deep in water was used, with beam energies from 246 up to 312 MeV/u.

Results

Alanine's response in a conventional therapy context

Figure 2 shows the dose-response curve for alanine pellets in the range between 5 e 40 Gy, for 6-MV photon beams. Each point refers to the mean signal of 4 pellets, and 4 measurements each (changing the orientation in the cavity to avoid potential anisotropic effects).

The comparison between FF and FFF conditions showed no significant differences, indicating that the detector could be used in both modes with a similar level of accuracy.

The linear fitting obtained in Figure 2 (FF condition, red line curve) was used as the calibration curve for the irradiation with protons and carbon ion beams. This differs from other studies in which the calibration curve was obtained with a ^{60}Co source from some primary standard laboratories, such as the National Institute of Physics, NPL in the United Kingdom (Fattibene et al. 2002; Carlino et al. 2018). In our case, it was obtained with therapeutical photons.

The ESR response was also evaluated in terms of angular dependence. This is important as the pellets have a cylindrical shape, and the angle of radiation incidence is likely to vary in clinical applications. Figures 3A and 3B show that there is no angular dependence for alanine, considering both a ‘planar’ geometry, in which rectangular phantom slabs are used, and a cylindrical geometry, in the case of the semi-cylindrical phantom.

Alanine's response in a Hadrontherapy context

Proton beams

Figure 4 shows the ESR alanine dose-response curve for proton beam irradiation (energy of 148.8 MeV), in the interval of doses from about 5 up to 45 Gy, measured in RW3 at 18 mm of depth. The ESR signal values were converted into dose values according to the fitting from Figure 2. The comparison was made with the dose obtained with the ionization chamber as a reference. The experimental curve was adjusted with a linear fitting as shown in the inset. Based on this, a variation of about 1.5% was found.

The analysis of the angular dependence did not demonstrate any dependence effect on the ESR signal, considering the same beam energy (Figure 5). Some fluctuation is observed around the mean value, but it is always within one standard deviation, which is about 0.5 Gy.

Figure 6 depicts the energy dependence analysis of the ESR signal, for protons irradiation, normalized by the dose obtained with the ionization chamber. The results showed an average response of 3% lower than expected, related to the dose estimation process for alanine, based on photon calibration. Therefore, the same dose for different source qualities may induce slightly different ESR signal intensities.

Figures 7A and 7B show the depth dose profile analyses for conventional Bragg and SOBP curves, respectively. The alanine response is compared to the ionization chamber. In the first case, it is observed that the closer the alanine pellet is to the peak, the greater the difference to the reference. At the peak position (151 mm deep), there is an underestimation of the dose with alanine above 20%. This behavior can be associated with high-LET effects in alanine, or quenching, which facilitates the processes of recombination and saturation as a consequence of the high energy release along the track (Hansen and Olsen 1989; Marrale et al. 2009).

The effect of high-LET radiation can be also observed in the SOBP profile (Figure 7B). If one considers the mean value obtained per depth position, there is a reduction trend in the alanine signal with the depth. Although the variation of doses is small, the difference in LET values is significant, which explains this behavior in the SOBP.

Carbon ion beams

Figure 8A shows the dose-response curve for alanine with respect to the ionization chamber one, for a 280 MeV/u carbon ion beam and doses up to 45 Gy. The linear fitting obtained has an angular coefficient of 0.923, which is lower than 0.985 (value obtained for protons). This indicates a greater difference to the reference detector, showing a response dependence on this specific particle type, not found for protons.

Energy dependence analysis is shown in Figure 8B. There is an average underestimation of the dose of around 11%. However, for high energy (at around 400 MeV/u), the estimated dose is the highest one, which would be associated with an energy dependence of alanine when irradiated with heavy particles as carbon ion beams.

Finally, Figure 9 presents the dose profile for an SOBP condition, with a flat dose distribution between 120 and 180 mm of depth. The pellets were allocated within this range, at depths of 125, 150, and 172 mm. The profile shows that, at the distal position, there is a strong quenching phenomenon due to the LET effect, similar to the observed for protons irradiation, reducing the value of the dose by about 30% in comparison to the reference.

Discussion

The results obtained in this study showed that ESR alanine pellets are reliable for use in dosimetry of different radiation qualities, including proton and carbon ion beams. In the case of the photons, our results showed a linear dose-response behavior over the entire range of doses analyzed and no angular dependence, as has been reported in previous studies (Bradshaw et al. 1962; Baffa and Kinoshita 2014). However, it has been also observed that the accuracy can vary depending on the dose-averaged LET of the proton and carbon ion beams, as shown when the signal is compared to a reference detector such as the ionization chamber.

Different from previous reports (Fattibene et al. 2002), this study constructed a calibration curve based on the therapeutical photons as shown in Figure 2. Either for FF or FFF condition, the experimental results were successfully fitted with a linear equation, obtaining an R-squared value above 0.999. Additionally, the fitting parameters are quite close between them, showing that there are no significant changes in response due to the use of these filters. The standard deviation was small, as the signal is expected to be reproducible in this range. It corroborates a previous study that reported relative uncertainty values below 0.5% can be found, for the range of doses of 5-25 Gy (Anton 2006).

The linearity of response with doses was also observed for proton and carbon ion irradiation. However, the comparison made with the ionization chamber has shown differences in response between both systems. With an underestimation of doses by using alanine. The first consideration to be made is regarding the calibration process. The signal obtained from alanine irradiation in a hadrontherapy context was used together with the photon irradiation-based calibration curve. Because of the LET characteristics of proton and carbon ion beams, there is an increased probability of both recombination and saturation (Hansen and Olsen 1985). These phenomena reduce the concentration of radicals that are measured by ESR, hence, apparently reducing the absorbed dose.

Onori et al. (1997), for example, evaluated the response of alanine to a 62 MeV proton beam at the Paul Scherrer Institut (PSI) in Switzerland and compared it to the ionization chamber response. Their results showed variations between 2 and 5% when comparing alanine doses (calibrated with a ^{60}Co source) with the ionization chamber ones. The mean ratio alanine/ionization chamber value was 0.97 for the dose range of 5-250 Gy. This is similar to the 1.5% found here (Figure 4). On the other hand, it is much lower than the 8% difference observed in the dose-response curve for carbon ions (Figure 8A). As for the dependence on the protons' energy, the variation of 3% is similar to the 4% obtained by Onori et al. (1997) for a dose of 10 Gy.

The findings of this study are also in agreement with the report of Ableitinger et al. (2013), which evaluated the use of alanine as a dosimeter in the auditing procedure of therapeutical light beams along with Monte Carlo (MC) simulations. In that case, the alanine ESR response was compared to other dosimetric systems, including radiochromic films and ionization chambers. The pellets were irradiated with both proton and carbon ion beams. Results showed a maximum deviation of – 3.6% and -4.7% for proton and carbon ions beams, respectively. In another similar study, the response of alanine to protons of different dose-averaged LETs between 1.44 and 2.49 keV/µm presented a decrease of up to 3.3 % for the highest LET value (De Saint-Hubert et al. 2021). Our analysis was performed in a slightly different interval of LETs (between 3 and 5 keV/µm), however, a similar reduction was found.

The major difference between the ESR signal and the reference was observed for carbon ion beams though, as shown in Figures 8 and 9. This is a direct consequence of the higher dose-average LETs in comparison to the proton ones, with values up to 100 keV/µm. In this regard, the study by Herrmann et al. (2011) made an extensive evaluation of the alanine response over a mean particle energy range from 70 up to 400 MeV/u, and how it differs from their proposed model. Their results of energy dependence showed that the lower the energy, the lower the effectiveness of the response, which is around 85% for mean particle energy of 70 MeV/u and reaching an effectiveness of about 95% for the upper limit (particle energy of 400 MeV/u). The results obtained here (Figure 8B) showed a mean effectiveness of 89% for the range between 150.7 and 398.8 MeV/u. Considering the different influencing parameters in the procedure adopted here, such as the difference in dose for each experimental point (energy value); and keeping the depth of the pellet, leading to different positions in the Bragg peak curve; the results agree.

The effect of the LET on the alanine response is clearly observed in the depth dose profiles (Figures 7 and 9), in which the quenching is pronounced. In the case of protons, a difference in doses obtained between alanine and the ionization chamber has been observed for the distal point by Onori et al. (1997). However, their measurements of alanine in SOBP showed a good agreement, with variations not greater than 6%, and values within one standard deviation, in comparison to the reference. In this work variations in the order of 10% are shown (considering the mean value of the experimental points over the whole curve range).

LET dependence, as commented, is evidenced in the carbon ion beam scenario. There was indeed a reduction in the alanine effectiveness in SOBP for carbon ion beam up to 35 % (Figure 8), which has been simulated and experimentally shown in a previous report by Herrmann et al. (2011) for a 270.55 MeV/u beam. In the same scope, the study of Ableitinger et al. (2013), showed a significant reduction in the relative effectiveness of EPR alanine due to the high-LET from carbon ions radiation, which was about 25% at the distal position of the field. This reduction was more pronounced than the 3.5% for the proton irradiation found in the same report.

These results emphasize that, although the use of alanine in dosimetry for therapeutical uses does not show main concerns in terms of dose rate, dose-response behavior, and energy dependence for photons (Bradshaw et al. 1962; Anton 2006; Desrosiers and Puhl 2009; Baffa and Kinoshita 2014), it has when dealing with high-LET and high-energy heavy particles. Therefore, appropriate corrections need to be taken into consideration.

Conclusion

This study showed the response of ESR alanine pellets in the context of hadrontherapy with protons and carbon ion beams, and its comparison to the response for photon radiation. The results were evaluated with respect to the reference detection system, which is the ionization chamber.

The ESR signal has a linear response over the range of about 5-45 Gy for all the radiation qualities assessed (photons, protons, and heavy ions), which was obtained with a photon radiation-based calibration curve. Despite the linearity, a decrease in effectiveness was observed for protons and carbon ion beams, which is associated with their high dose-averaged LET characteristic. This induces processes of recombination, and further, underestimation of the doses.

Evaluations of the alanine for depth dose profile analysis in Bragg and SOBP conditions have shown an underestimation of the absorbed doses by up to 30 %, due to quenching effects. For carbon ion beams, this effect is even more pronounced as energy-dependence effects take place. The results show the versatility of alanine but also reinforce the issues that need to be addressed for its use in hadrontherapy.

Acknowledgments

This work has received funding from the Italian Ministry of Research with the Project "SiciliAnMicronanOTecH Research And Innovation CEnter "SAMOTHRACE" (MUR, PNRR-M4C2, ECS_00000022), spoke5-Università degli Studi di Palermo "S2-COMMs - Micro and Nanotechnologies for Smart & Sustainable Communities" and by the European Union-NextGeneration EU, accompanied by the Mission, Component and CUP of the project. "Funded by the European Union-NextGeneration EU, Mission 4 Component 2 Inv. 1.5 CUP B83C22003930001.

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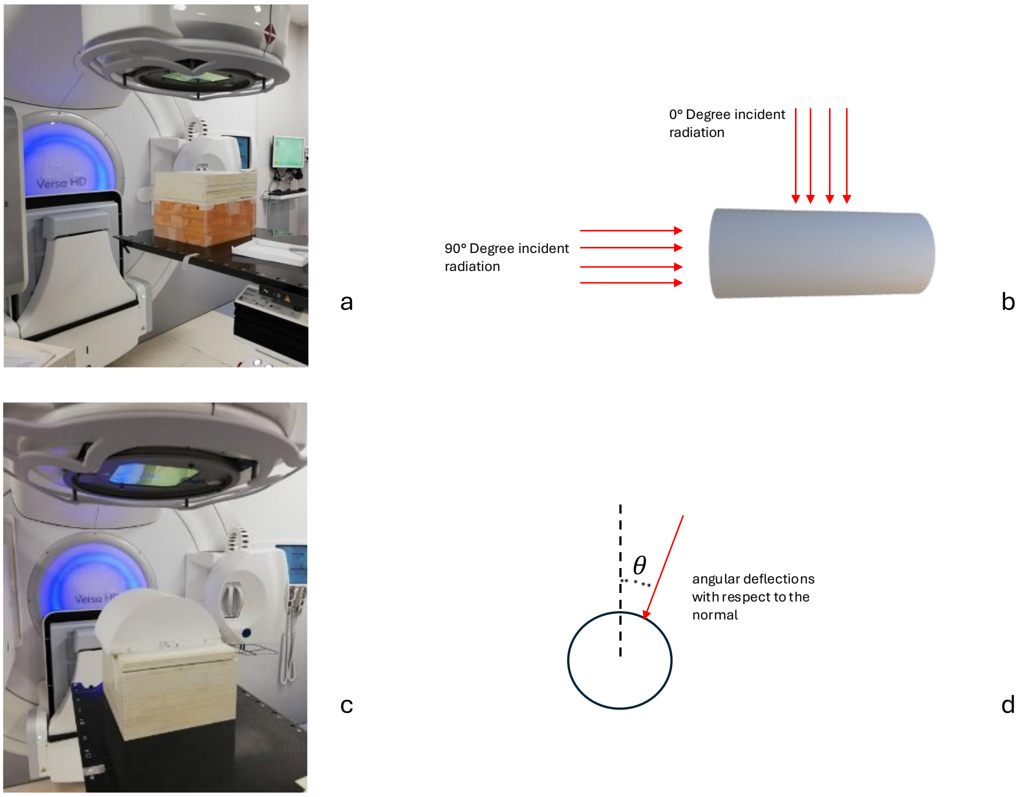


Figure 1. Irradiation geometries for photon beams are depicted in panels (a-b) for planar geometry and (c-d) for cylindrical geometry. RW3 slabs were utilized to simulate human tissue as the medium. A semi-cylindrical phantom was employed to maintain consistency in the irradiation path within the cylindrical configuration (panel c).

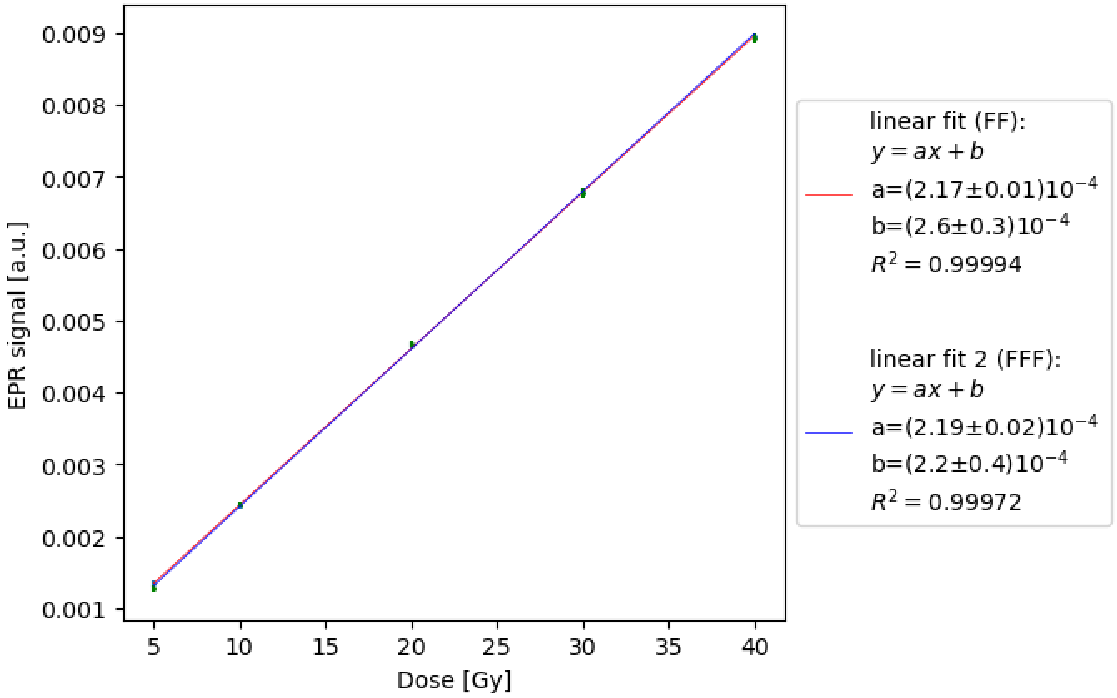
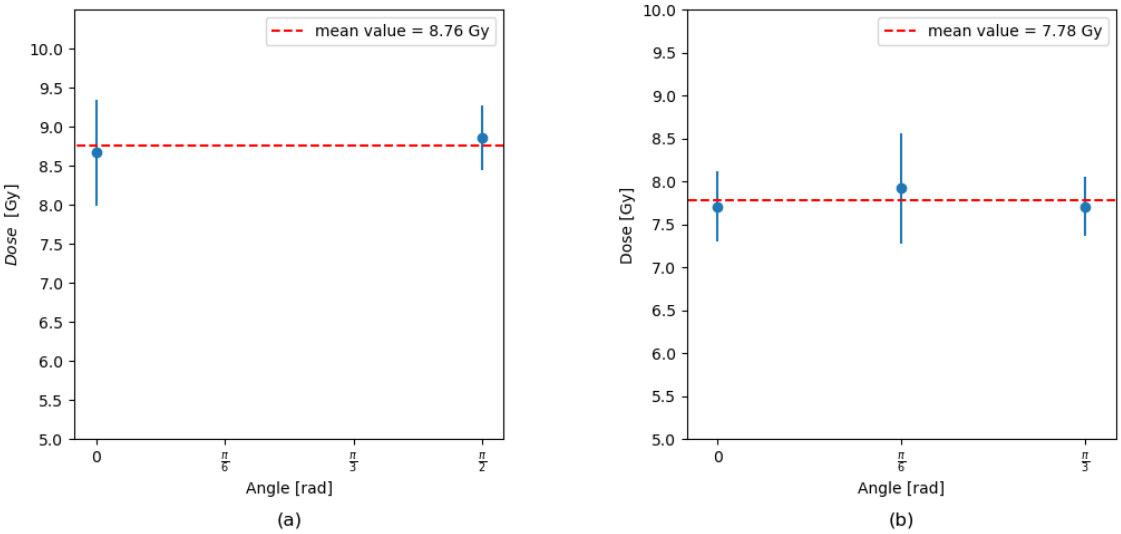


Figure 2. Calibration curve of ESR alanine signal, for photon irradiation in the range between 5 and 40 Gy, considering FF and FFF conditions. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation. Note that the standard deviation is small and may not be clear in the scale (the highest value obtained was $5 \cdot 10^{-5}$ at 5 Gy).



(a)

(b)

Figure 3. Angular dependence for alanine pellets evaluated for photon irradiation, considering (A) a planar and (B) cylindrical configuration. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation.

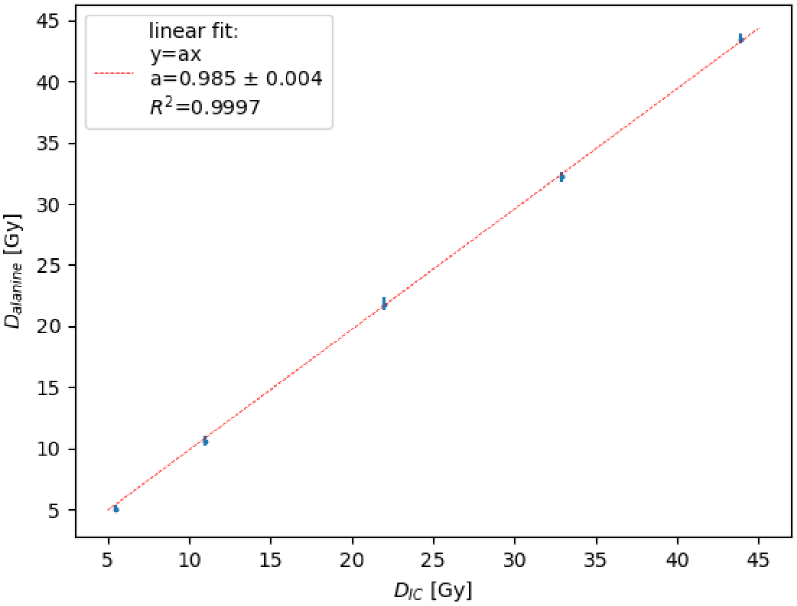


Figure 4. Dose-response curve of ESR alanine signal as a function of the ionization chamber response. Measurements for proton irradiation (beam energy of 148.8 MeV, alanine at 18 mm deep in RW3), in the range between 5 and 45 Gy. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation. Note that the standard deviation is small and may not be visible in the plot (values varied between 0.1 to 6 %, with the highest obtained at 5 Gy).

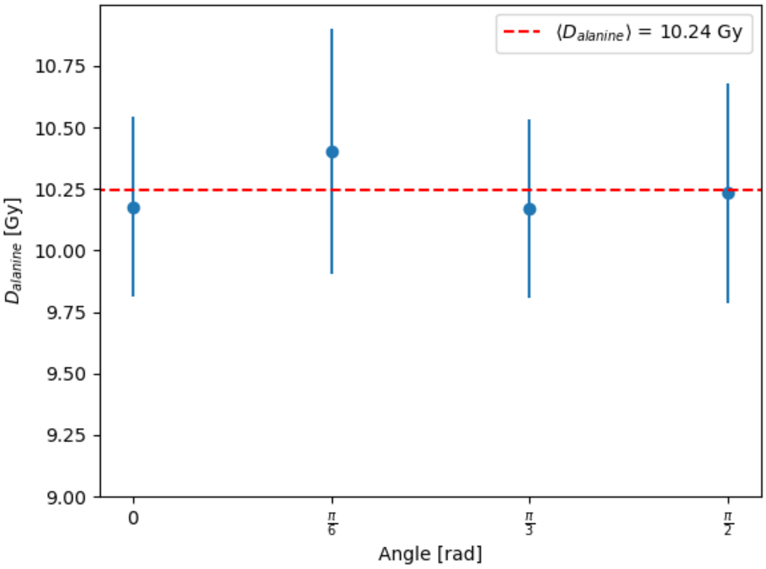


Figure 5. Angular dependence for alanine pellets after proton irradiation compared to ionization chamber, considering a cylindrical configuration. Beam energy of 148.8 MeV, and pellets allocated at 18 mm depth in RW3. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the

orientation in the cavity), while error bars stand for the respective standard deviation (the highest value obtained was 0.5 Gy).

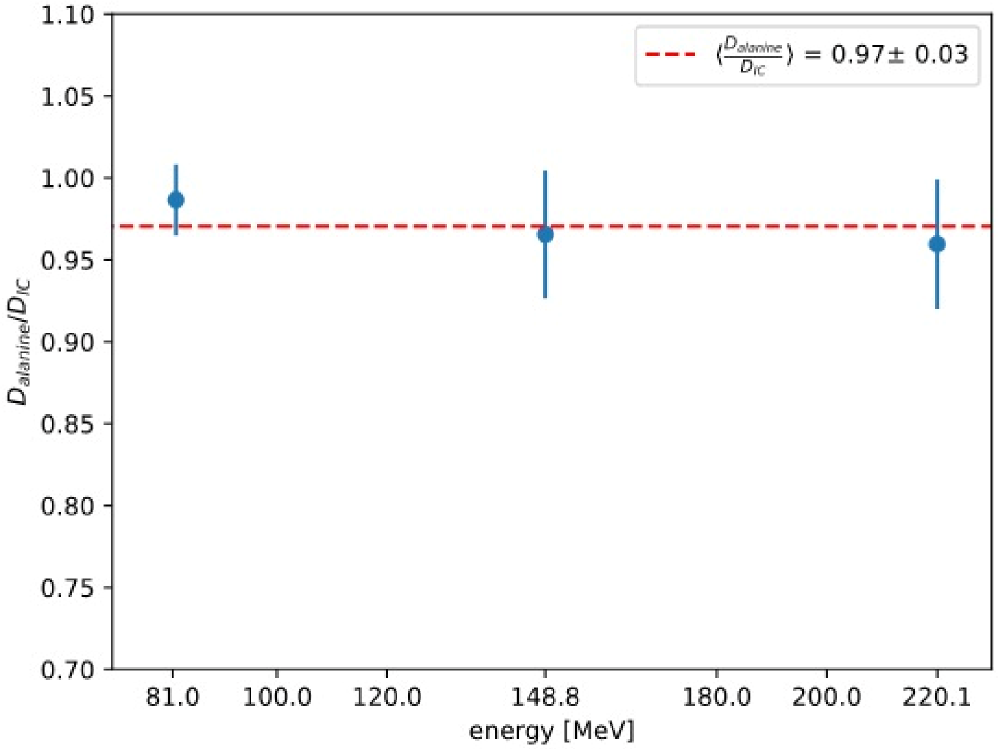
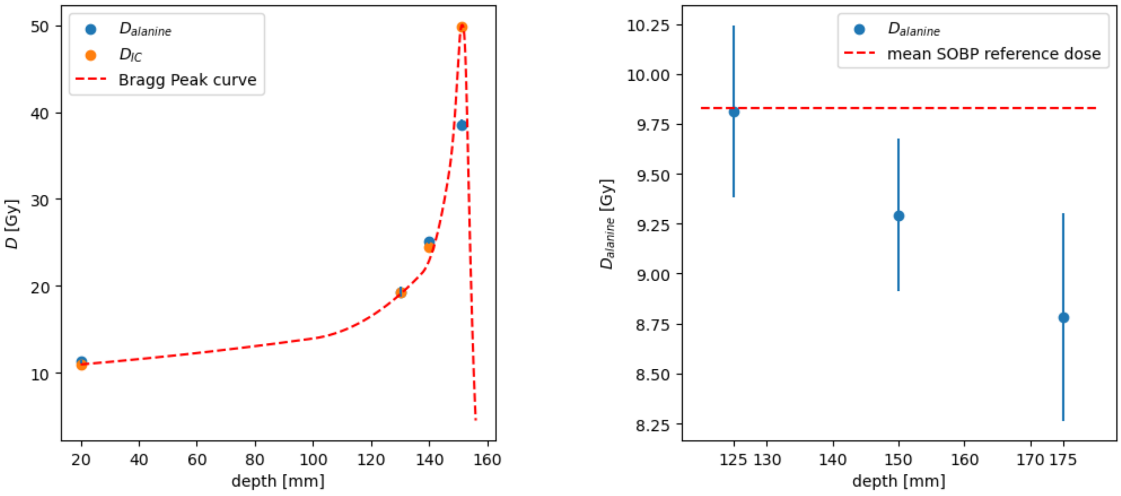


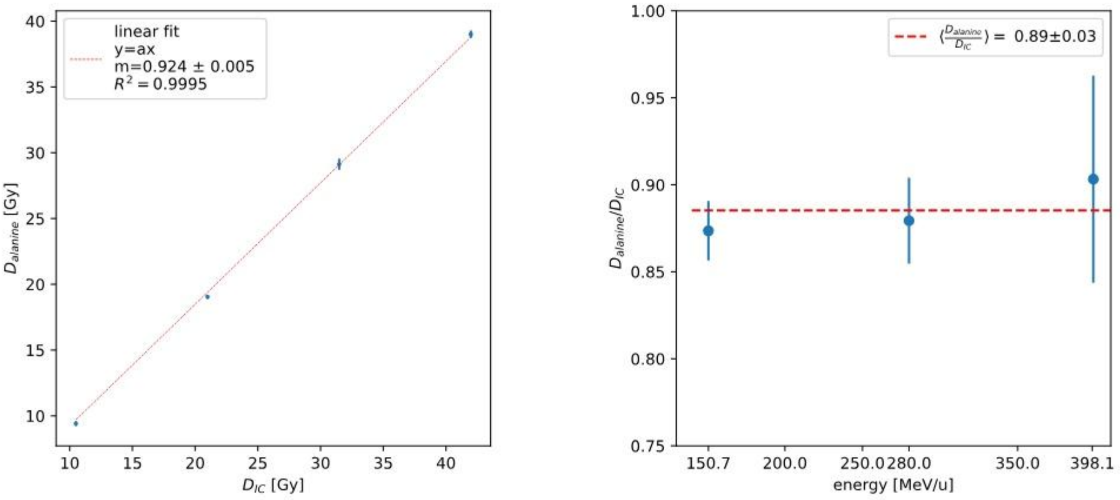
Figure 6. Energy dependence for alanine pellets after proton irradiation compared to ionization chamber, considering a cylindrical configuration. Proton beam energies between 81.6 and 220. 1 MeV/u. Pellets were allocated at 18 mm depth in RW3. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation.



(a)

(b)

Figure 7. Depth-dose profile for alanine pellets in comparison to ionization chamber for (A) Bragg peak and (B) SOBP conditions, with proton beam irradiation. The dashed line in part (B) refers to the mean reference dose for the flat region in SOBP (obtained with an ionization chamber). Each experimental point refers to the mean value of 12 measurements (3 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation.



(a)

(b)

Figure 8. (A) Dose-response curve of ESR alanine signal in function of the ionization chamber response. Measurements for carbon ion beam irradiation (beam energy of 280 MeV/u), in the range between 5 and 45 Gy. And (B) energy dependence for carbon ion beam irradiation (beam energies between 150.7 and 398.8 MeV/u). Alanine pellets were allocated at 18 mm depth in RW3 in both cases. Each experimental point refers to the mean value of 16 measurements (4 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation. Note that the standard deviation is small and may not be clear in the scale.

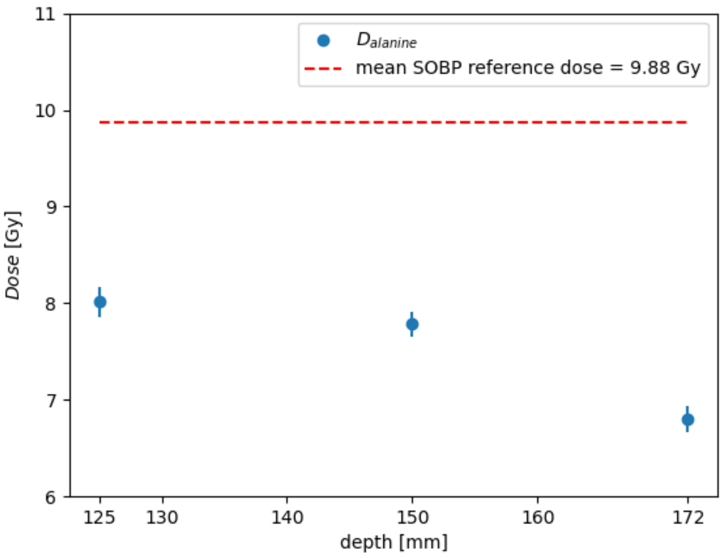


Figure 9. Dose depth profile for alanine pellets in comparison to ionization chamber for SOBP condition with carbon ion beam irradiation. Beam energies varied between 245.8 and 311.8 MeV/u. Each experimental point refers to the mean value of 12 measurements (3 pellets and 4 measurements each, by changing the orientation in the cavity), while error bars stand for the respective standard deviation.