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Systematic analysis of alanine/EPR pellets for reference dosimetry with UHDR electron beams for FLASH radiotherapy

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ABSTRACT

Advancements in radiotherapy techniques, such as FLASH radiotherapy, in which ultra-high dose rates (UHDR) are applied, have set a challenge in investigating whether the standard dosimetric systems used in conventional radiotherapy can still be used without further issues. In this context, it is necessary to understand how passive dosimeters, e.g., alanine based on electron paramagnetic resonance (EPR), respond to these UHDR conditions. Therefore, this study aimed to systematically analyse the use of alanine pellets under FLASH conditions. The pellets were irradiated with electron beams at 7 and 9 MeV from an ElectronFlash LINAC. The response was evaluated in terms of percentage depth dose (PDD) and as a function of dose per pulse (DPP). Experimental data are compared to Monte Carlo (MC) simulations and with a diamond detector as the reference detector. A good agreement between MC-simulated and experimental PDDs was found (variation <3 % for the 7 MeV beam). The alanine/EPR signal presented a linear response as a function of DDP, up to values of about 7 Gy/pulse, and no dose-rate dependence. In addition, average instantaneous dose rates were successfully estimated for different LINAC setups. These findings highlight the potential use of both MC simulations and alanine dosimeters in the planning and monitoring of delivered doses in the context of FLASH radiotherapy.

1. Introduction

Ionising radiation is widely used in different applications covering environments such as industries, hospitals, nuclear power plants, and research institutes. In medicine, it has long been essential in the diagnosis and treatment of diseases, as is the case of radiotherapy. In the last decade, especially, a promising technique using ultra-high dose rates (UHDR) for values above 40 Gy/s has been described, in a modality denominated FLASH radiotherapy (or FLASH-RT). In this regard, as with any sort of radiotherapy, it is important to ensure both accuracy in dose delivery and safety to the employees, which is performed by means of dosimetry. This study focuses on the usability of a well-established passive detector, based on the electron paramagnetic resonance (EPR) of alanine, in this new context.

The relevance of FLASH-RT increased with the pioneer study of Favaudon et al. (2014), which showed differences in the induction of pulmonary fibrosis in mice when thoracic-irradiated with a single fraction of 17 Gy (dose rate of 0.03 Gy/s), and when dose rates between 40 and 60 Gy/s were used. The improvement brought by FLASH-RT lies in the reduction of toxicities observed in normal tissue compared to

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conventional radiotherapy (CONV-RT), whilst maintaining the anti-tumoral response. In addition, due to its elevated dose rates, FLASH-RT allows for entire treatment doses or large dose fractions to be delivered in less than a few seconds, which is much shorter than the several minutes taken in a conventional procedure (Durante et al., 2018; Harrington, 2019; Wilson et al., 2020; Romano et al., 2022). The possible underlying mechanisms that explain the effectiveness of FLASH-RT over CONV-RT have been a focus of discussion within the scientific community, although the main hypothesis has attributed it to oxygen depletion in irradiated tissues (Wilson et al., 2020).

The major novelty of FLASH-RT is its potential to enhance the therapeutic window (Durante et al., 2018). However, it came along with the necessity of not only understanding how and why this modality offers improved results, but also the need for investigating and establishing new protocols and apparatus, and appropriate real-time dose monitoring and dosimetry. The UHDR poses a challenge in the monitoring of doses because most methods employed in CONV-RT use detectors that are considerably affected by these dose rates, and due to high doses per pulse (DPP), both characteristics of the FLASH therapy, resulting in non-linearity and saturation effects in ionisation chambers, for example (Romano et al., 2022).

Amongst the radiation detectors currently used in medical dosimetry, and therefore, established for use under CONV-RT conditions, one might mention ionisation chambers (International Electrotechnical Commission, 2011; Low et al., 2011; Hourdakis et al., 2016), luminescent dosimeters based on thermoluminescence (TL) and optically stimulated luminescence (OSL) (Bos, 2001; Yukihara and Kron, 2020), Fricke gels (Schulz et al., 1990; d'Errico et al., 2017), and radiochromic films (Chu et al., 1990; Devic et al., 2016), for example. Another dosimetric system, which has been extensively utilised, is based on EPR, in which the signal is proportional to the concentrations of free radicals induced by ionising radiation and has been applied to the detection of different radiation beams (Regulla and Deffner, 1982; Ikeya, 1993; Nagy, 2000; Schauer et al., 2006; Schaeken et al., 2011).

Although the EPR signal from materials such as polycrystalline formates and dithionates (Lund et al., 2005; Danilczuk et al., 2008; Gustafsson et al., 2011), tartrates (Yordanov and Gancheva, 2004; Brai et al., 2007; Marrale et al., 2014; Brustolon et al., 2015), phenolic compounds (Gallo et al., 2015) and others (Mikou et al., 2015; Santos et al., 2018; Cano et al., 2021) has been long studied, crystalline l-α-alanine remains as the main and standard EPR material for both transfer (Sharpe et al., 1996; Khoury et al., 2015) and secondary standard dosimetry (Anton, 2005; Desrosiers et al., 2008) in the majority of laboratories.

The use of alanine is justified by its good metrological characteristics, including production of stable free radicals due to ionising radiation; a dose-response linear from absorbed doses of 2 Gy up to 10^5 Gy; effective atomic number close to that of the human tissue, meaning tissue equivalence for electron and photons irradiation; a non-destructive read-out procedure (different from other passive dosimeters, such as TLDs); low fading at room temperature; and small energy dependence for values above 100 keV (Kojima et al., 1992; Arber and Sharpe, 1993; Marrale et al., 2008; Anton et al., 2013).

As for other commonly used detectors in medical dosimetry, at first, the use of alanine was established based on CONV-RT, in which the doses are delivered at a rate of about 0.1 Gy/s. First studies in the 1980s, and therefore, much before the advent of FLASH, showed an independence of the EPR signal from the dose rate. Regulla and Deffner (1982) demonstrated the absence of dose-rate dependence in the range from 0.02 Gy/s up to around 3 Gy/s, considering absorbed doses from 5×10^3 Gy up to 3.5×10^5 Gy. This upper limit of dose rate was further increased to 10^8 Gy/s by the same authors (Regulla and Deffner, 1983). Kudoh et al. (1997) evaluated the EPR signal response in comparison to radiochromic films and found independence from dose rates up to 3×10^{10} Gy/s (absorbed doses in the order of kGy). Later, though, it was observed that the use of alanine for doses higher than 5 kGy can lead to a significant dose-rate effect, which starts to be significant for dose rates at around 1 Gy/s. No rate effects were detectable for doses below 1 kGy (Desrosiers et al., 2008). Moreover, it was pointed out that the irradiation temperature (i.e., the temperature during the irradiation) that is commonly elevated for high-dose electron beams seems to weaken the dose-rate dependence (Desrosiers and Puhl, 2009).

With the development of FLASH-RT, investigations on the response of passive dosimeters, including alanine, which seems not to have a strong dependence on the dose rate (in comparison to active ones such as ionisation chambers), have been more commonly reported in the last couple of years. Jorge et al. (2019) investigated the response of three types of passive dosimeters, namely TLDs, alanine, and radiochromic film, after irradiation with a high-dose prototype linear accelerator (LINAC) type Oriatron 6e (Ert6), with a pulsed electron beam of 6 MeV. The absorbed doses estimated by these detectors were found to be within 3 % of variation, for dose rates of 0.078, 210, and 1050 Gy/s (total absorbed dose $<$20 Gy). Similarly, Bourgouin et al. (2020) used alanine/EPR after irradiating with a LINAC at the Metrological Electron Accelerator Facility (MELAF) in the German National Metrology Institute (PTB). Accurate dosimetric measurements with alanine were successfully carried out for different DPP values, showing a linear dose response for DPPs up to 2.4 Gy.

Jorge et al. (2022) did a dosimetric comparison using passive dosimeters, including alanine. The study was performed with three different LINACs, two at the CHUV in Switzerland (Elekta from Synergy and Oriatron eRT6), and one at Stanford (Varian Trilogy medical LINAC). DPPs up to 3.5 Gy and average dose rates up to 420 Gy/s were used. Alanine's relative bias was between −2 and 0 % (comparing expected and measured doses). Gu et al. (2024), also with alanine, showed that the absorbed dose was within 5 % of deviation and with less than 1 % variation in repeatability when using an Elekta LINAC with an electron beam of 6 MeV, doses up to 50 Gy, and instantaneous dose rates up to 8×10^8 Gy/s. In the context of UHDR, alanine also showed reliability when compared to its signal after ^{60}Co irradiation with a dose rate of around 0.3 Gy/s and using synchrotron X-ray (dose rate of 11.6×10^3 Gy/s), for a dose range of 40–5000 Gy (Soliman et al., 2020).

Given the importance of a good agreement between delivered doses and the planned ones for successful diagnosis and treatments in medicine (Andreo, 2018), given this demand for dosimetric systems that can cope with the UHDR used in FLASH therapy, further investigations on the use of detectors already established for CONV-RT are fundamental. Therefore, this study aimed to investigate the response of EPR alanine pellets exposed to UHDR electron beams at dose rates up to 10^6 Gy/s in the context of FLASH. This response was evaluated in terms of DPP and compared to the one obtained with a diamond detector, the so-called FLASH diamond (fD), which was specifically designed for FLASH-RT applications (Marinelli et al., 2022, 2023). Additionally, different irradiation setups, considering the applicator diameter and distance from the applicator, were carried out, in which alanine pellets were used to estimate the instantaneous dose rates.

Considering the context of FLASH-RT, the percentage depth dose (PDD) is an essential parameter in treatment planning. Therefore, the alanine response results as a function of PDD were compared with Monte Carlo (MC) simulations. These simulations were used to calculate the energy released within the alanine pellets via radiation. This combined use of MC and alanine spectroscopy allows for better identifying whether there are dose-rate dependence effects or not.

2. Materials and methods

2.1. Irradiation setup

Irradiations were carried out with the UHDR electron beams accelerated at 7 and 9 MeV from the research-dedicated ElectronFlash LINAC (SIT-Sordina, IORT Technologies, Italy) at the SIT Sordina facility and the Centro Pisano for FLASH Radiotherapy (CPFR), as exemplified in

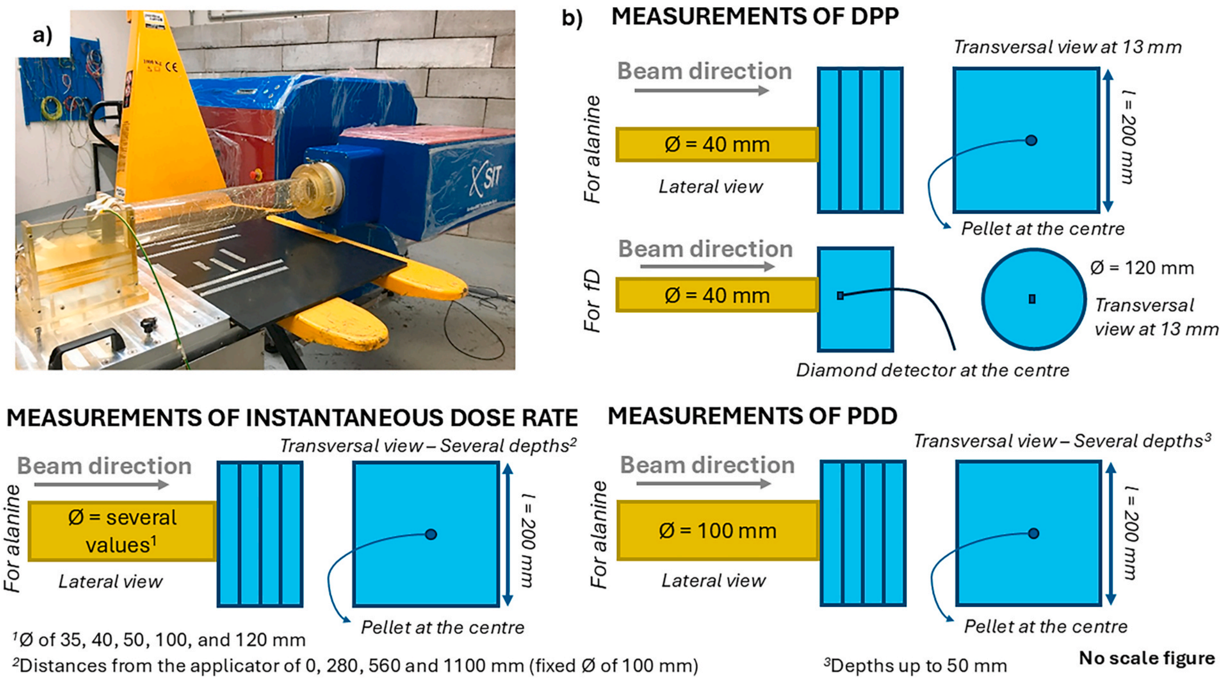

Fig. 1. (a) Setup of the ElectronFlash LINAC (SIT-Sordina, IORT Technologies, in Aprilia, Italy), in which it can be seen the accelerator unit on the right (coupled to the applicator). And (b) scheme for the different configurations of irradiation for alanine and diamond detector (fD): measurements of instantaneous dose rate, dose per pulse (DPP), and percentage depth dose (PDD). The items in blue refer to the PMMA phantom/slab, while the yellow item refers to the collimator. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 1a. The single pulse duration was set to 4 μs (it can vary from 0.5 to 4 μs), and the DPP was varied from 0.1 up to 7 Gy, corresponding to a maximum reached dose rate per pulse (instantaneous dose rate) of 1.75 $\times$ 10^6 Gy/s. Gafchromic™ EBT-XD radiochromic films were placed onto the surface of the Polymethylmethacrylate (PMMA) phantom for measuring the entrance dose as a controlling step.

The DPP measured with the alanine pellets was compared to the one measured with the flash diamond (fD) detector, currently considered the reference dosimeter in FLASH radiotherapy (Marinelli et al., 2022, 2023), using the 9 MeV UHDR electron beams accelerated at the CPFR. The alanine dosimeters were irradiated within a PMMA phantom at the build-up position, i.e., at 13 mm depth corresponding to the position of the maximum dose in the depth dose distribution, using the 40 mm diameter applicator, while the fD was placed at the same depth into a cylindrical PMMA phantom of 120 mm diameter (Fig. 1b) - more details are described in the report by Marinelli et al. (2022). The DPP was varied by changing the beam current, i.e., the charge per pulse, by using the triode gun of the ElectronFLASH LINAC installed at the CPFR.

The measurement of the PDD was carried out at the Aprilia SIT Sordina facility, with the alanine pellets positioned at the centre of the field, i.e., right after the final PMMA 100 mm diameter, 1000 mm long, 5 mm thick applicator. The pellets were inserted in PMMA slab plates, which were perpendicular to the beam direction, as well as the flat bases of the pellets (Fig. 1b). In particular, the alanine pellets were placed within a PMMA phantom, in a stack configuration to sample the dose at different depths, and irradiated at a constant instantaneous dose rate during the pulse of about 350 kGy/s, at depths up to 50 mm. The resulting PDD curves for both 7 and 9 MeV were then compared to MC simulations, as shown in the next sections.

Moreover, for evaluating the alanine pellets response as a function of the instantaneous dose rate with both 7 and 9 MeV, the pellets were also irradiated in Aprilia using different applicator diameters of 35, 40, 50, 100 and 120 mm, and also varying distances between the end of the applicator and the pellets from 0 to 280, 560 and 1110 mm (in this case, keeping fixed the applicator diameter at 100 mm).

2.2. Dosimetric systems

EPR measurements were carried out using commercial alanine pellets, in cylindrical form from Gamma-Service Produktbestrahlung GmbH (Germany). The pellets' dimensions are 4.8 mm in diameter, 3.0 mm in height, 68 mg in mass, and a density of 1.26 g/cm^3 (Marrale et al., 2016).

The EPR signal from radiation-induced free radicals was acquired with a Bruker Elexsys E580 spectrometer equipped with a cylindrical cavity and operating in the X-band (microwave frequency of about 9.80 GHz). The measurement parameters included a field sweep width of 30 mT, sweep time of 42 s, microwave power of 2.99 mW, modulation amplitude of 1 mT, and 4 accumulated scans (the parameters of microwave power and modulation amplitude were previously investigated to obtain these optimised values) (Milluzzo et al., 2024; Romeo et al., 2025). EPR intensity was measured through the height peak-to-peak (h_{pp}) of the central line, following the established in the literature (Regulla and Deffner, 1982; Arber and Sharpe, 1993). For each dosimeter, the EPR measurement was carried out four times, varying the position of the pellet inside the cavity, to deal with possible anisotropy effects. The values are given as the mean of these four measurements and the respective standard deviation.

The reconstruction of absorbed dose values was based on a calibration curve obtained with a 6 MV X-ray irradiation, in the range of 5–40 Gy, and fitted with a linear equation. The EPR signal was normalised to the pellet mass.

Gafchromic™ EBT-XD radiochromic film (Ashland Inc., Bridgewater, NJ, USA) was used for comparison. Its response was analysed using the software from the same manufacturer. The reading was carried out in an Epson Expression 12000XL (Epson, USA). The signal obtained by each channel was converted to a net optical density (OD), and the sensitometric curve was calculated. The use of the film was solely for quality control of the beam uniformity.

FLASH diamond detector, or fD, is a detector conceived by Marinelli et al. (2022, 2023), modified from the already commercial PTW 60019 microDiamond (mD) detector, to be applied in FLASH-RT. The detector presents a linear response up to a DPP of 20 Gy/pulse, and a signal non-dependent on the electron beam PRF (in the range from 5 up to 245 Hz, corresponding to average dose rates from around 2 up to 960 Gy/s). The fD was used as the reference dosimeter during the experiment described here.

2.3. Monte Carlo simulations

Monte Carlo simulations were carried out using the Geant4 (GEometry ANd Tracking) toolkit to realistically reproduce the experimental setup and predict the experimental dose distributions (Agostinelli et al., 2003; Allison et al., 2006, 2016). In particular, the eFLASH_radiotherapy Geant4 advanced example, already included in the official distribution of the Geant4 code and developed by the INFN-CT division, was used for the simulations. The code realistically models the ElectronFlash LINAC from the SIT company, including the final plastic applicators and the realistic electron source in terms of energy and angular distributions. The code was also validated against experimental data as reported in Arce et al. (2025). The Geant4.10.07 version was used for the simulations, setting as electromagnetic physics list the opt_4, considering the low-energy electrons involved. As the cut-off energy, a range cut of 0.1 mm was set, meaning energy cuts of approximately 91.6, 92.9 and 1.12 keV, for electrons, positrons, and gamma rays, in PMMA. These values were obtained from interpolating the tabulated data from the National Institute of Standards and Technology (NIST), and considering the electromagnetic transport model adopted. Cross-section values were also obtained by interpolating data from NIST and the International Atomic Energy Agency (IAEA).

The setup used for the alanine irradiation was simulated within the code, as shown in Fig. 2. In particular, a stack of alanine pellets was simulated within a cylindrical 20 cm diameter 6 cm thick PMMA (density = 1.19 g/cm^3) phantom placed at the exit of the plastic applicator. The PMMA phantom was attached to the applicator. Each alanine pellet was modelled as a separate alanine (density = 1.25 g/cm^3) 2.4 mm radius, 3 mm thick cylinder with the flat side facing the beam. A 2.5 × 2.5 mm^2 source of 108 electrons was simulated as input with the realistic energy and angular spectrum provided by the SIT company. The dose released in each alanine pellet was retrieved using the native scorers implemented in Geant4.

3. Results and discussion

3.1. Response of alanine under UHDR conditions used in FLASH-RT

Fig. 3 shows the DPP measured with the alanine pellets compared with the ones measured with the FLASH diamond detector in the same conditions, for DPP ranging from 0.1 up to 7 Gy, corresponding to an instantaneous dose rate of about 1.75 × 10^6 Gy/s in the latter case. As shown, an excellent agreement was found, as demonstrated by the parameters resulting from the linear fit of the data points, with an angular coefficient close to 1 (R^2 = 0.9997) and an intercept of −0.017. The percentual difference was within 2.5 %, except for the lowest DPP. The result indicates that alanine has a linear response with the DPP at least up to around 7 Gy and can measure the absolute dose at these extreme instantaneous dose rates, as demonstrated by the agreement with the FLASH diamond.

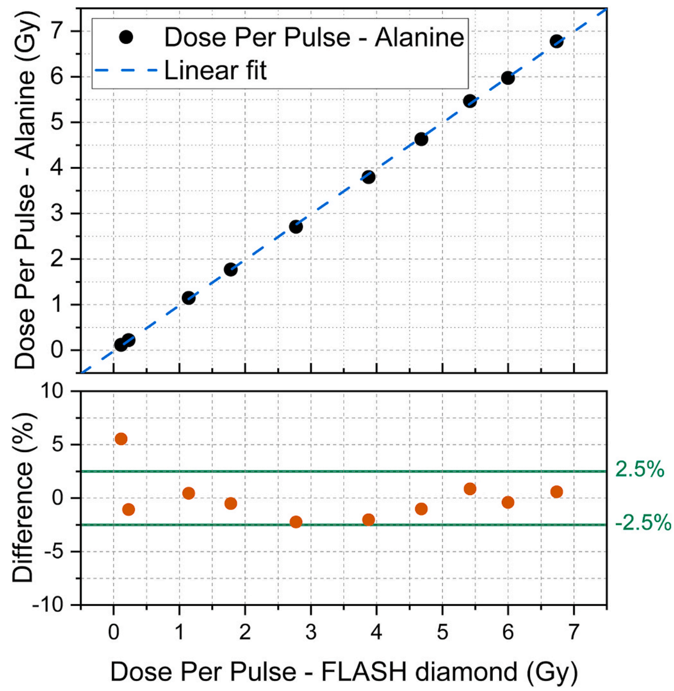

Fig. 3. Dose per pulse (DPP) measured by alanine/EPR as a function of the DPP measured using the FLASH diamond detector. The pulse duration used was 4 μs.

The findings from our study corroborate previous reports that have evaluated the extended use of alanine pellets as reference dosimeters also in FLASH-RT. Whilst some detectors, mostly the active ones, such as ionisation chambers (considered the "gold standard" in CONV-RT), in which the UHDR hampers their use and requires either large correction factors or a search for new designs, for passive detectors (including alanine and luminescent dosimeters based on TL and OSL), the issues seem less and easier to deal with (Romano et al., 2022; Di Martino et al.,

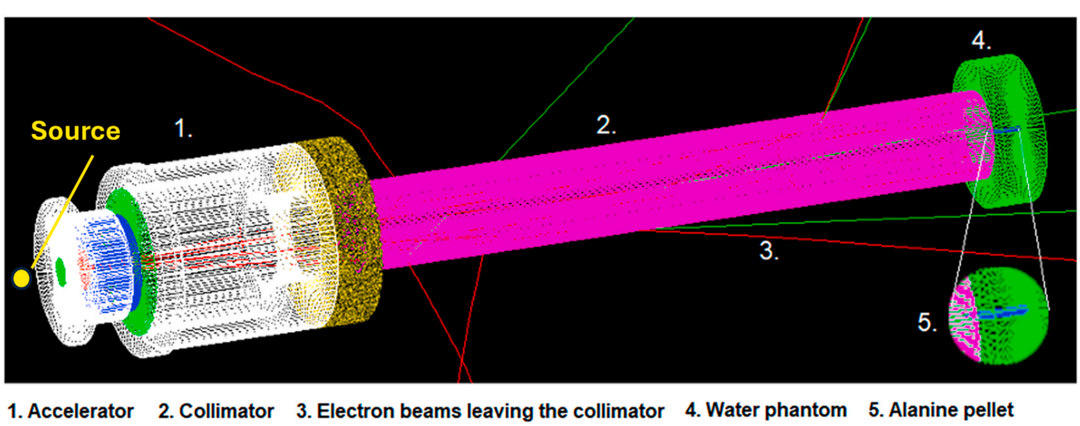

Fig. 2. The setup used for the Monte Carlo simulation via Geant4 with reference to the experimental setup. In the figure are shown (1) the accelerator, (2) the collimator, (3) some electron beams leaving the collimator following a random path (represented by the lines), (4) the PMMA phantom, and (5) the zoom view of the PMMA phantom highlighting the position of the EPR alanine pellet.

2022). Although in the case of the alanine pellets, a readout post-irradiation is needed, meaning they are not suitable for real-time and in vivo dosimetry, there is the advantage of bringing the accumulated experience from decades of use in CONV-RT.

As reported in Jorge et al. (2019), for example, three different setups were used to irradiate mice's total body, zebrafish embryos, and mini-pigs with UHDR electron beams using the Oriatron eRT6 LINAC. The study evaluated the absorbed dose ratio *R*, given by the dose estimated via the ionisation chamber divided by the mean dose of three passive dosimeters (alanine, radiochromic films, and TLD). As a result, deviations up to 8 % were found. This deviation is greater than the one observed in our study for the comparison between FLASH diamond and alanine (<6 %). The better accuracy here can be associated with the excellent properties of the designed diamond detector to operate under UHDR, but also due to the reliability of alanine.

Regarding the alanine response as a function of the DPP with UHDR pulsed electron beams, Bourgouin et al. (2020) demonstrated the linearity of the alanine response up to 2.4 Gy, showing promising use in FLASH conditions. This upper limit was demonstrated here to be higher and reaches at least 7 Gy per pulse.

Analysing different irradiation configurations available in the LINAC, Fig. 4 shows the results of the dose rate obtained through the alanine EPR signal (the instantaneous dose rate was obtained by dividing the total dose by the pulse width, i.e., 4 μs). It can be observed that there is a decrease in the dose rate with increasing values of the applicator's diameter (Fig. 4a). This behaviour is due to the particle scattering with the inner wall of the applicator. For smaller diameters, there is an increase in the electron scattering, which leads to a concentration of dose at the centre, where the pellets are allocated. By changing the diameter from 35 to 100 mm, the dose rate drops to less than half.

A similar trend is observed when analysing the dose rate as a function of the distance from the applicator (Fig. 4b). This decrease is associated with the reduction of particles' fluence reaching the alanine pellets.

In both analyses, the dose rate variation with the applicator diameters for the beams at 7 and 9 MeV has the same trend, indicating that similar processes occur. The difference is noticed only in terms of dose rate, which is higher for the 9 MeV electron beam.

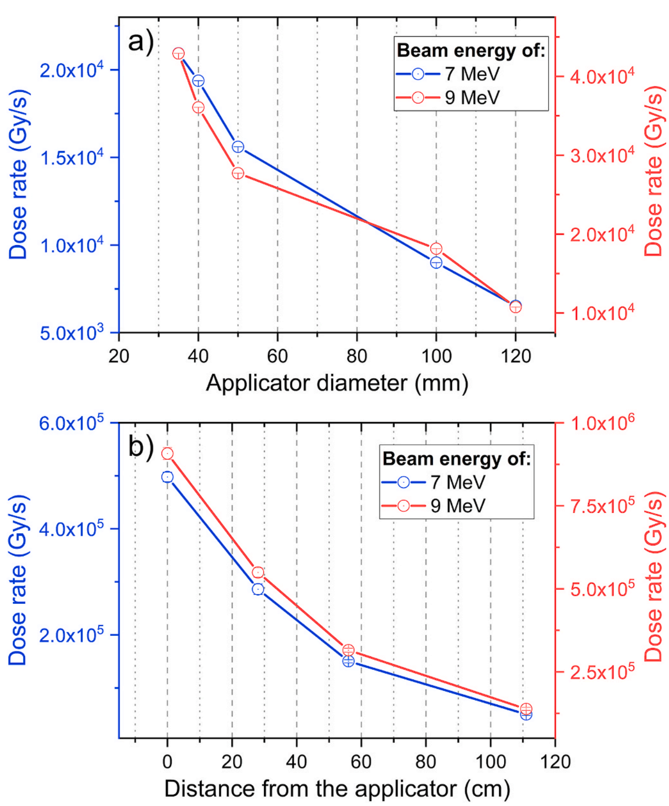

Fig. 4. Instantaneous dose rate values measured by alanine detectors. The response is given in terms of absorbed dose. The dose rate was obtained by dividing the total dose by the sum of pulse durations considering (a) applicators of different diameters and (b) different distances between the applicator and the alanine pellets. The mean values refer to the measured dose by alanine EPR signal from three pellets (each measured at four orientations), whilst the error bars refer to the standard deviation. In all cases, the pulse duration used was 4 μs.

3.2. *Comparison of the measured PDD with MC simulation*

Fig. 5a depicts the comparison between the PDD curves obtained through MC simulation and from the alanine/EPR signal, for an electron beam at 7 MeV. There is a good agreement between both curves (variation within 5 % over the entire range studied), indicating that not only was the simulation validated by the EPR results, but also that the EPR signal has no noticeable dose-rate dependence effect (the dose rate per

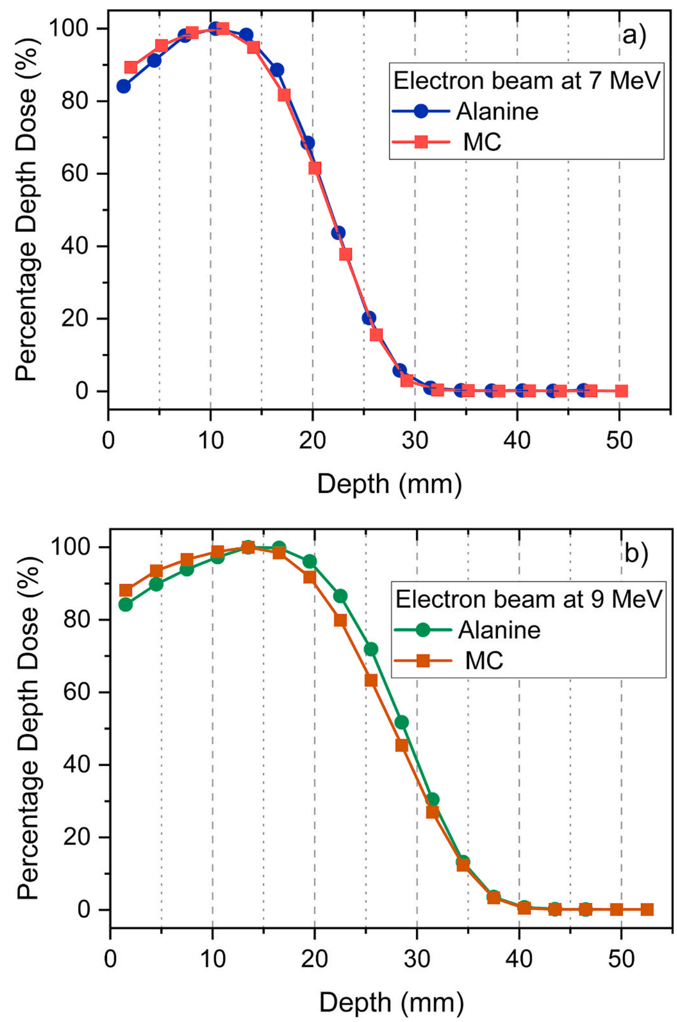

Fig. 5. Comparison between the Percentage Depth Dose (%) values obtained by Monte Carlo (MC) simulation and alanine/EPR signal for an electron beam of (a) 7 and (b) 9 MeV. For the MC, it was considered a collimator of 910 mm in length and 120 mm in diameter. The dose rate per pulse is about 350 kGy/s (with a pulse duration of 4 μs). The EPR signal refers to the average signal of the four measurements of the same aliquot (one for each orientation regarding the normal of the tube inserted in the cavity, in which in the centre is the dosimeter). The EPR standard deviation was within 0.40 %; thus, the error bars were not plotted as they would not be seen in this scale.

pulse was approximately 350 kGy/s). For PMMA depths <10 mm, it can be noticed that the MC simulation values are above the ones found by EPR. This difference can be due to the inaccurate consideration of low-energy scattered electrons by the MC simulation, which are more relevant at the entrance (i.e., due to the energy cut for electrons of about 92 keV).

For the analysis considering an electron beam at 9 MeV, higher variations are observed between the MC simulation values and the ones obtained with EPR (Fig. 5b). As observed for the case with a 7 MeV electron beam at the entrance, an overestimation of the dose computed by the MC simulations can be observed. However, for deeper positions, for PMMA depths ranging from 20 to 35 mm, the MC values are below the ones estimated by EPR. A possible hypothesis relies on the presence of secondary electrons, which are created in the process of irradiation, inside the applicator, and are not totally considered as a range cut of 0.1 mm was implemented in the simulation (as described in Section 2.3).

Studies approaching experimental data obtained from FLASH protocols and comparisons with MC simulations have been more recently conducted and have shown a good agreement between them, which allows for validating the MC models used. This is an important step towards accurate dose distribution and monitoring in FLASH-RT. Lazarus et al. (2022), for example, obtained replication of electron beams from a Siemens LINAC using MC simulation, within a criterion of 3 %/3 mm. Different electron beam energies and applicators were considered, and the dose was evaluated in terms of PDD. And more recently, a comprehensive and detailed benchmarking study by Arce et al. (2025) has demonstrated the reliability of the Geant4 simulations, in the framework of biomedical applications, including the eFLASH_radiotherapy model used in this work.

The response of EPR/alanine has been compared to the simulated results obtained through MC simulations, for different purposes, with good agreement. One might cite, for example, the use for estimating the output factors of electron beams in a LINAC (Marrale et al., 2015). However, there is still a gap in reports in which the response of alanine has been used to validate specific MC simulations in the FLASH context.

3.3. On the potential use of alanine in FLASH-RT

The use of UHDR characteristic of the FLASH modality is the major concern when investigating the use of already established radiation detectors. Even before the advent of FLASH-RT, there were concerns about the dependence of alanine/EPR signal on the dose rate, which raised discussions that started in the 1980s. Since then, the hypothesis of non-dependence on dose rate has become more convincing, and the present study aligns with it. However, the important aspect that needs to be taken into account when analysing dose-rate dependence on alanine is not only this effect itself (in an isolated form) but also another key parameter, which is the total absorbed dose. As it stands up to date, the effect due to dose rate is meant to be pronounced for higher doses, in the order of 10^3 Gy (Desrosiers et al., 2008). Therefore, further investigations should deal with FLASH conditions and high absorbed doses to try to observe some effect.

The findings of this study corroborate with previous studies in which non-dependence has been found. Furthermore, the experimental and simulated results were obtained in FLASH-RT conditions, using doses not higher than typical treatment doses (which are far from the limit of 10^3 Gy reported), hence, allowing us to consider that alanine has the potential to remain a reliable dosimeter in radiotherapy, be it in conventional mode or be it in FLASH mode.

4. Conclusions

This study has successfully investigated the response of commercial alanine EPR pellets for electron beams operating at UHDR in the FLASH-RT modality, in combination with MC simulations, to calculate the energy released inside the detector.

Alanine EPR response was compared to the response of the FLASH diamond detector, for the interval of doses per pulse from 0.1 up to 7 Gy. The result indicated that alanine does not show any dose-rate dependence within this range. Furthermore, the absorbed doses of alanine pellets were in agreement (discrepancy <6 %) with those estimated by the FLASH diamond detector used as reference.

The use of alanine pellets was also successful in estimating the instantaneous dose rate for different irradiation setups, in which the effects of the applicator's dimensions and sample positioning were observed.

The use of MC simulations allowed for estimating the PDDs for electron beams of 7 and 9 MeV, produced by the ElectronFlash LINAC (SIT-Sordina, IORT Technologies, Italy). The results obtained by simulation were compared with the alanine EPR response, showing a good agreement, with a variation below 5 %, at least for an electron beam at 7 MeV, therefore, the model was validated. As for the case with an electron beam at 9 MeV, the variation between simulation and experimental data was higher, which pointed out the necessity of updating the MC model for further investigations, probably considering the contribution of secondary electrons more accurately.

The results of this study corroborate previous reports in the literature, showing that alanine is promising to have its use extended from CONV-RT, which is already widely applied, to UHDR regimens, and therefore, in FLASH-RT (Desrosiers et al., 2008; Jorge et al., 2019, 2022; Bourgouin et al., 2020; Gu et al., 2024). It has been demonstrated by the absence of dose-rate dependence effects (and for absorbed doses within the therapeutic range) and assisted by the MC simulation results.

This study has some limitations in its approach in terms of evaluating the alanine/EPR response to a wide range of doses, doses per pulse, and pulse widths, for example. Therefore, further studies should take these aspects into account and consider investigating the alanine/EPR response to different doses under FLASH-RT regimen, although a linear response may be expected; the response for the same given dose under different pulse width delivery conditions; and the lateral dose profile along with the PDD. Additionally, the robustness of the dosimetric system could be analysed with an intercomparison amongst different laboratories, which in turn, can facilitate protocol establishment.

CRediT authorship contribution statement

M.C. D'Oca: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **A. de Farias Soares:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **G. Collura:** Methodology, Investigation. **G. Milluzzo:** Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **E.R.A. Castronovo:** Formal analysis, Data curation. **D. Del Sarto:** Investigation. **F. Di Martino:** Methodology, Investigation. **G. Felici:** Methodology, Investigation. **L. Masturzo:** Methodology. **J.H. Pensavalle:** Methodology, Investigation. **F. d'Errico:** Investigation. **F. Romano:** Methodology, Investigation, Formal analysis, Data curation. **M. Marrale:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Felice, G. reports a relationship with S.I.T. Sordina IORT Technologies S.p.A. that includes: employment. Pensavalle, J.H. reports a relationship with S.I.T. Sordina IORT Technologies S.p.A. that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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