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Absorbed-dose-to-water measurement using alanine in ultra-high-pulse-dose-rate electron beams

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Keywords: alanine dosimetry, UHPDR, Monte Carlo, electron beam, integrating current transformer (ICT)

Abstract

Objective. The aim of the presented study is to evaluate the dose response of the PTB's secondary standard system, which is based on alanine and electron spin resonance (ESR) spectroscopy measurement, in ultra-high-pulse-dose-rate (UHPDR) electron beams. *Approach*. The alanine dosimeter system was evaluated in the PTB's UHPDR electron beams (20 MeV) in a range of 0.15–6.2 Gy per pulse. The relationship between the obtained absorbed dose to water per pulse and the in-beamline charge measurement of the electron pulses acquired using an integrating current transformer (ICT) was evaluated. Monte Carlo simulations were used to determine the beam quality conversion and correction factors required to perform alanine dosimetry. *Main results*. The beam quality conversion factor from the reference quality ^{60}Co to 20 MeV obtained by Monte Carlo simulation, 1.010(1), was found to be within the standard uncertainty of the consensus value, 1.014 (5). The dose-to-water relative standard uncertainty was determined to be 0.68% in PTB's UHPDR electron beams. *Significance*. In this investigation, the dose-response of the PTB's alanine dosimeter system was evaluated in a range of dose per pulse between 0.15 Gy and 6.2 Gy and no evidence of dose-response dependency of the PTB's secondary standard system based on alanine was observed. The alanine/ESR system was shown to be a precise dosimetry system for evaluating absorbed dose to water in UHPDR electron beams.

1. Introduction

FLASH treatment is a radiotherapy modality in the early stages of development. This modality aims to deliver the total prescribed dose to the patient within a few seconds rather than minutes by using ultra-high-pulse-dose-rate (UHPDR) beams, i.e. ionizing radiation with a dose per pulse much larger than that used in conventional radiotherapy. The instantaneous dose rate, or the dose rate within the pulse, is about three orders of magnitude larger than the dose rate used in conventional radiotherapy. The dose delivered with a single radiation pulse ranges from 0.6 Gy to 10 Gy. This technique is promising as it has already shown some advantages over radiotherapy treatments that apply conventional pulse doses in the order of 1 mGy. Multiple investigations (Favaudon *et al* 2014, Montay-Gruel *et al* 2018, Montay-Gruel *et al* 2019, Wilson *et al* 2020) have shown that delivering the same dose used in conventional treatment but doing so within seconds instead of minutes reduces adverse side effects to healthy tissue (the so called FLASH effect). However, dosimetry has proven challenging as the ion chamber response is no longer linear with the dose rate due to large ion recombination effects that do not follow the approximate theoretical behaviour valid at conventional pulse doses (Petersson *et al* 2017, McManus *et al* 2020). With the aim of improving dosimetry for UHPDR, a research project funded by the European Union

within the framework of the EMPIR programme was launched in September 2019 (Schüller *et al* 2020). An important part of this project is the investigation and development of primary and secondary absorbed-dose measurement standards for UHPDR electron beams.

A large amount of pre-clinical research into the FLASH effect is performed in UHPDR electron beams (Favaudon *et al* 2014, Bourhis *et al* 2019, Schüler *et al* 2022). The characterization of UHPDR electron beams is most often based on passive dosimeters, such as radiochromic film, alanine or TLDs. Radiochromic film has the advantage that it can be used for relative dose measurement and simultaneously for absolute dose measurement (Jaccard *et al* 2017, Petersson *et al* 2017, Schüler *et al* 2017, Lempart *et al* 2019, Konradsson *et al* 2020, Szpala *et al* 2021), and it has shown consistency with TLD. However, the uncertainty found in a clinical study remained high at 4% (Jaccard *et al* 2017, Konradsson *et al* 2020), and most measurements are performed in a plastic phantom rather than directly in water.

Absorbed-dose-to-water measurement with alanine has a lower uncertainty compared to film and TLDs, namely less than 1.0%, at the conventional dose rate (McEwen *et al* 2015). Alanine pellets have a small sensitive volume and alanine's radiation transport properties are nearly equivalent to water (Anton 2006). Alanine is therefore a good candidate for establishing a secondary absorbed-dose measurement standard for UHPDR electron beams. Alanine is however a passive dosimeter, which has the disadvantage that real-time measurement is not possible, and measurements are time consuming. Alanine provides no or only limited information on the beam's shape.

Alanine dosimeters are already used as a reference in UHPDR electron beams (Jorge *et al* 2019, Bourgouin *et al* 2020, Soliman *et al* 2020, Kranzer *et al* 2021) since no dose per pulse dependency is expected in a UHPDR beam (Kudoh *et al* 1997). However, there is a lack of study of UHPDR electron beams for the dose-per-pulse range between 0.1 Gy and 10 Gy at the uncertainty level required for clinical purposes. Jorge *et al* (2019) have shown an agreement within 3% with radiochromic film and TLDs, with a quoted uncertainty of 2% for alanine. They concluded that alanine shows a linear response; however, only two doses per pulse were evaluated, namely 2.1 Gy and 10.5 Gy. Gondré *et al* (2020) studied alanine response between 20 Gy and 100 Gy and quoted a 1.54% uncertainty. Here, however, the dose per pulse was not reported.

The present investigation aims to evaluate the PTB alanine and electron spin resonance (ESR) spectroscopy system as a secondary standard for absorbed-dose-to-water measurement in the UHPDR reference electron beam (Bourgouin *et al* 2022). To do so, Monte Carlo simulations were used to calculate the field correction factor that accounts for beam profile non-uniformity, and to determine the beam quality conversion factor, $k_{\mathrm{Al.,E}}$ (McEwen *et al* 2020). The combined relative standard uncertainty of the PTB alanine/ESR secondary standard measurement system was evaluated in the context of UHPDR electron beam dosimetry. The in-beamline charge measurement of the electron pulses was performed using an integrating current transformer (ICT). As the dose delivered per pulse was expected to be linear with the number of charges accelerated per pulse, on the condition that the other beam parameters remain unchanged, the measured charge per pulse during alanine measurement was used to evaluate the expected dose per pulse response independence of alanine dosimeters.

During this investigation, a diamond detector prototype (B1) (Kranzer *et al* 2022) was used in parallel with the absolute dose measurement performed with alanine to measure the lateral beam profile in the vicinity of the measurement position. A commercially available diamond detector was not used because a saturation effect in the UHPDR electron beam has been observed in such detectors (Di Martino *et al* 2020). The value of the field correction factors derived from the spatial information of the beam measured with the detector was compared to the value obtained by Monte Carlo simulations.

2. Material and methods

2.1. Absolute dosimetry with alanine

Absolute dose measurement in PTB's UHPDR electron beams is achieved using the PTB alanine dosimetry secondary standard. Alanine is an amino acid that is typically used in the form of small pellets with a binding agent. When alanine is exposed to ionizing radiation, stable free radicals are created in direct proportion to the total absorbed dose. The concentration of these free radicals can be detected by means of electron spin resonance (ESR) spectroscopy. The absorbed dose to water, $D_{\mathrm{Al,w}}$, obtained with the alanine/ESR secondary standard dosimetry system (Anton 2006) is determined using the following equation:

$$D_{\mathrm{Al,w}} = \left(\frac{A_{\mathrm{det}} \cdot k_{\mathrm{env}}(T)}{m_{\mathrm{det}} \cdot \mathscr{A}_{D,w}^{^{60}\mathrm{Co}}} \right) k_{\mathrm{Al.,E}} \cdot k_{\mathrm{field}}, \tag{1}$$

where A_{det} is the signal amplitude of the alanine pellet measured with the ESR spectroscopy system, m_{det} is the mass of the alanine pellet, and $k_{env}(T)$ is the correction factor to account for the temperature during measurement. $\mathscr{A}_{D,w}^{^{60}Co}$ is the dose-normalized amplitude, i.e. the normalized signal amplitude of an alanine pellet by the known absorbed dose that has been delivered. This value is obtained by measuring the amplitude of alanine pellets irradiated in a reference ^{60}Co beam and comparing the result to a known absorbed dose to water traceable to the water calorimeter, PTB's primary standard (Krauss 2006). $k_{Al.,E}$ is the beam quality conversion factor which will be discussed below. A correction factor, k_{field}, has been added to account for the beam radial non-uniformity.

The alanine used in this study was in the form of white cylindrical pellets made of 90.9% amino acid L-alpha alanine in a 9.1% paraffin wax binder (Harwell, UK). The pellets had an average mass of 60(2) mg, a diameter of 4.8(1) mm, a height of 2.8(1) mm and a density of 1.184 g·cm^{-3}. The concentration of the alanine-free radicals was read with a Bruker EMX 1327 ESR spectrometer system (Bruker, MA, United States). The details of the PTB's ESR system can be found in Anton (2006). During irradiation, a total of eight pellets were vertically stacked in a sealed PMMA sleeve which mimics a Farmer ion chamber shape (see Farmer design in figure 3 of Anton (2006)). To determine the absorbed dose to water from alanine, the average dose measurement from the eight pellets was used. The PMMA-alanine assembly used during measurement to evaluate $\mathscr{A}_{D,w}^{^{60}Co}$ is the same as the one used for measurement in UHPDR electron beams. The uncertainty of the alanine absorbed-dose measurement in ^{60}Co is between 0.4% and 0.6% (Anton 2006).

The alanine dose response in an electron beam is known to be different than that in the ^{60}Co photon beam used for calibration. For this reason, the alanine dose measurement in the electron beam was corrected using the beam quality conversion factor, $k_{Al.,E}$, which has a consensus value of 1.014(5) (McEwen *et al* 2020). In the current investigation, this value will be redetermined for PTB's UHPDR electron beams using Monte Carlo simulation as detailed in section 2.4.

As the dose response of alanine is known to depend on the temperature during irradiation, the water temperature in the phantom was recorded using a PT100 platinum resistance temperature sensor during the irradiation process. To ensure temperature equilibrium throughout the alanine pellets, the PMMA-alanine assembly was immersed for 10 min before being exposed to about 15 Gy. The correction factor, $k_{env}(T)$, was applied to measurements in order to account for the temperature (McEwen *et al* 2015):

$$k_{env}(T) = 1 - c_T \cdot (T - T_0), \tag{2}$$

where c_T is a constant equal to 1.9(2) 10^{-3} K^{-1}, T_0 is the reference temperature, 293.15 K, and T is the water temperature during measurement. More details about alanine dosimetry in electron beams, calibration in the ^{60}Co photon beam, and the associated uncertainties can be found in the literature (Anton 2006, Vörös *et al* 2012, Anton *et al* 2013, McEwen *et al* 2020).

The field correction factor, k_{field}, is defined as the ratio between the dose deposited in a single alanine pellet centred in the radiation beam at the reference point of measurement and the average dose deposited in eight pellets stacked vertically in the beam at the reference depth z_{ref}. This correction factor was added because the lateral dose profile was not uniform in the PTB's UHPDR electron beams, which have an approximated Gaussian lateral dose distribution shape. As such, the average signal of the eight irradiated alanine pellets (contained in the holder resembling a Farmer chamber) would have led to an underestimation of the absorbed dose to water at the reference point of measurement. Moreover, during measurement, the PMMA-alanine assembly was positioned in the water tank using the laser system in the experimental room. The beam centre is known not to be aligned with the laser system within 3 mm (Bourgouin *et al* 2022), and it shifts by about 1 mm between the different linac settings used to change the dose per pulse. As the PMMA-alanine assembly is not symmetric in the horizontal and vertical directions, the field correction factor, k_{field}, can be separated into two correction factors, $k_{field,v}$ and $k_{field,h}$, for vertical and horizontal, respectively.

The vertical field correction factor, $k_{field,v}$, can be directly obtained with the alanine measurement, since eight pellets are irradiated in that direction. This correction factor is obtained using the ratio of the relative signal of the pellet positioned at the reference point measurement to the average signal of the eight pellets. It can also be estimated from Monte Carlo simulations or from lateral beam profile measurements. As concerns the horizontal field correction factor, $k_{field,h}$, it cannot be obtained through alanine measurement in the current setup because only one pellet is irradiated in the horizontal direction. As such, $k_{field,h}$ was estimated based on horizontal beam profiles measured with a diamond detector prototype and was compared to values obtained by means of Monte Carlo calculation.

2.2. Electron beam characteristics and monitoring

The Metrological Electron Accelerator Facility (MELAF) (Schüller *et al* 2019) of Germany's national metrology institute, PTB, is equipped with a research linear accelerator (linac). It can produce pulsed electron beams with a dose per pulse between 0.15 Gy and 6.2 Gy in a water phantom using two beam setups for a beam energy of

20 MeV at the linac exit window (Bourgouin *et al* 2022). The linac exit window is a 100 μm copper plate. The pulse repetition frequency is 5 Hz, and the pulse duration is 2.5 μs. The instantaneous dose rate is therefore between 0.06 Gy μs^{-1} and about 2.5 Gy μs^{-1}, and the average dose rate between 0.75 Gy s^{-1} and 30 Gy s^{-1}.

The beam is monitored using an in-flange integrating current transformer (ICT) (Bergoz, Saint-Genis-Pouilly, France) (Schüller *et al* 2017). The ICT signal has been cross calibrated against the absolute charge measurement using a Faraday cup. The ICT signal has been shown to be able to non-destructively measure the total charge of individual beam pulses (Schüller *et al* 2017), which is typically between 30 nC and 230 nC. A type B standard uncertainty of 0.015 nC ($k = 1$) is achieved combined with an estimated type A standard uncertainty for random fluctuation of about 0.1% on average.

The beam setup with the lowest dose-per-pulse range, 0.15 Gy to 0.9 Gy, is a setup in which the water tank's front window is positioned 90 cm from the linac exit window (defined as the source to surface distance [SSD] value). In addition to the copper exit window, the electron beam travels through a 2.0 mm scattering aluminium plate positioned 0.76 cm from the window. This beam will here be referred to as beam setup SSD90–02. The second electron beam setup, with the highest range of dose per pulse between 1.0 Gy and 6.2 Gy, will be referred to as beam setup SSD70–00. In this setup, the water tank is positioned 70 cm from the linac exit window and no additional scattering plate is used. Both beams have an approximated Gaussian lateral dose distribution at the reference depth z_{ref} in the water phantom with a full width at half maximum (FWHM) of 208(1) mm and 82(1) mm for the SSD90–02 and SSD70–00 setups, respectively. Although the relative energy fluence spectrum of the two beam setups are different due to the additional scattering plate for setup SSD90–02, the reference depth, z_{ref} (International Atomic Energy Agency 2000), of both beams is 46.5(3) mm in water based on Monte Carlo calculation (Bourgouin *et al* 2022). This can be explained by the larger field size for beam setup SSD90–02 compared to the SSD70–00 setup.

An adjustable in-beamline slit positioned after the linac bending magnet is used to vary the electron fluence in the linac beamline for the two beam setups. This directly impacts the dose deposited per pulse at the reference depth. The slit width has a small effect on the measured beam centre (about 1.0 mm) and on the full width at half maximum (FWHM) of the lateral dose profile measured at z_{ref} in water (about 2.0 mm). Furthermore, changing the slit width affects the divergence of the beam in the vacuum linac beamline, which causes a small deviation from a linear relationship between the number of charges accelerated per pulse, i.e. the ICT signal, and the absorbed dose at the reference point when the slit width is varied. The maximum deviation from linearity is expected to be smaller than 4% based on Monte Carlo simulation (Bourgouin *et al* 2022).

2.3. Irradiation procedure and relative dose measurement

The absorbed-dose-to-water measurements were performed for a range of dose per pulse in December 2020 using the SSD70–00 electron beam setup, and twice between April and June 2021 (five weeks apart) for both the SSD70–00 and SSD90–02 beams. For each of the two electron beam setups, six different doses per pulse were measured (the pulse dose was varied by changing the width of the in-beamline slit), giving a total of 12 measurements between 0.15 Gy and 6.2 Gy per pulse. For each dose-per-pulse setting, the alanine was irradiated with an absorbed dose of approximately 15 Gy, so each measurement required a different number of pulses to be delivered.

The irradiations of alanine were performed in a water tank positioned at the respective SSD, which was measured using a laser range finder ($\pm$3.0 mm, Bosch, Gerlingen, Germany). As PMMA has been shown to quickly degrade in UHPDR electron beams, the water tank used in this project was a modified 30 cm $\times$ 30 cm $\times$ 30 cm PMMA water tank in which the entrance beam window was replaced by a 0.776 cm thick clear polycarbonate plate. A 3D positioning system was used to position the PMMA-alanine assembly at the reference depth, and the alanine assembly was aligned in the orthogonal direction of the beam using the room laser system.

As mentioned earlier, the alanine measurements provide only limited spatial information about the lateral dose distribution and are time consuming. For this reason, further measurements of the relative dose distributions were performed throughout the course of this investigation to validate the beam stability and to monitor the beam centre position and beam size. The detector used was a diamond detector prototype (B1) suitable for UHPDR measurement that was developed at the Rome Tor Vergata University in collaboration with PTW Freiburg (Kranzer *et al* 2022). A diamond detector was selected for relative measurement because it has a small sensitive volume and real-time measurement is possible. A prototype was selected rather than a commercially available detector, as commercial devices have shown unwanted saturation effect when used in UHPDR pulsed beams (Di Martino *et al* 2020). The detector prototype is a diamond Schottky diode, which due to its smaller active volume (0.7 mm in diameter and 1.0 μm thick) has reduced sensitivity compared to the commercially available diamond detector. This, combined with a reduced series resistance, serves to avoid the saturation effect.

For both electron beams and for each linac slit width used to change the dose per pulse, a horizontal and vertical beam profile were measured at the reference depth along with a depth dose measurement carried out in parallel with alanine measurements. The results of the beam characterization and the beam stability were presented by Bourgouin *et al* (2022). The profile measurements were used to determine the field correction factors, $k_{\text{field,v}}$ and $k_{\text{field,h}}$, to be compared with values obtained from Monte Carlo calculations and, in the case of $k_{\text{field,v}}$, also with the alanine measurement.

2.4. Monte Carlo

Monte Carlo models of PTB's linac were created using the `EGSnrc` software toolkit, release v2020 (Kawrakow *et al* 2000). The `EGSnrc` model was used to obtain the alanine beam quality conversion factor, $k_{\text{Al.,E}}$, as it can be geometry dependent (Anton *et al* 2013) and the field correction factors, $k_{\text{field,v}}$ and $k_{\text{field,h}}$. To obtain $k_{\text{Al.,E}}$, the alanine to water dose ratio in the UHPDR electron beam is divided by the ratio of the same quantities in the reference ^{60}Co beam.

For the ^{60}Co beam and both electron beam setups (SSD70–00 and SSD90–02), the absorbed dose to alanine was simulated to be the dose deposited in the eight alanine pellets. The absorbed dose was then calculated using the average value across the eight pellets. The effect of the presence of the PMMA sleeve and the alanine pellets pile on $k_{\text{Al.,E}}$ was evaluated by simulation for both the ^{60}Co beam and the electron beams. To do so, the dose to alanine was first simulated for a geometry without PMMA sleeve and then simulated for a geometry with only a single centred pellet at the reference depth in water.

The model for the ^{60}Co beam was a collimated source with the energy fluence spectrum from Mora *et al* (1999) available with the `EGSnrc` distribution. The source's target shape was a 10 cm $\times$ 10 cm square field at 100 cm from the point source. A water cube of 30 cm $\times$ 30 cm $\times$ 30 cm was simulated 95 cm from the point source and the absorbed dose to water was calculated for a cylindrical scoring volume of 0.1 cm thick by 0.25 cm radius centred at a depth of 5 cm. The beam model for the electron beam was presented in Bourgouin *et al* (2022). The `EGSnrc` beam model was benchmarked against the relative dose measurement with the diamond detector prototype used in this investigation. The water scoring volume for the electron beam was a cylindrical volume of 0.1 cm thick by 0.10 cm radius centred at the z_{ref} depth, 4.65 cm. The water scoring volume radius was selected to avoid any volume averaging effect while minimizing computational time. The type A (statistical) standard uncertainty limit was set to 0.05%, which is typically 10^{10} particles for the ^{60}Co beam simulations and 10^{9} particles for electron beam simulations. Particles were tracked down to a kinetic energy of 5 keV, and no variance reduction was used.

To simulate water, the `water_icru90` density correction file included with the `EGSnrc` distribution was used. As the alanine pellets used at PTB are made of 90.9% amino acid L-alpha alanine and 9.1% paraffin wax binder, the alanine density correction files were generated by modifying the pure alanine correction files available with the `EGSnrc` distribution. The nominal density was changed from 1.424 g·cm^{-3} to 1.184 g·cm^{-3}. The chemical composition was modified to include 9.1% paraffin wax binder. The density correction was unchanged as the density correction factor calculated from crystalline density should be used (Anton *et al* 2013). The effect of the simulated density and chemical composition on the obtained $k_{\text{Al.,E}}$ was evaluated by comparing the results obtained using both density correction files (the customized file and the one provided in the `EGSnrc` distribution).

3. Results and discussion

3.1. Beam conversion and correction factors for the PTB UHPDR electron beam

For both UHPDR electron beam setups (SSD90–02 and SSD70–00), the beam quality conversion factor, $k_{\text{Al.,E}}$, calculated from Monte Carlo simulations was found to be on average 1.010(1). The value obtained is therefore 0.4% smaller than the consensus value of 1.014(5) (McEwen *et al* 2020), but remains within the standard uncertainty of the consensus value. As compared to the custom file, the use of the alanine density correction file available in the `EGSnrc` distribution was found to reduce the absorbed dose to alanine by −0.63(7)% for the ^{60}Co beam and −0.55(7)% for electron beams. Therefore, since $k_{\text{Al.,E}}$ is calculated as the ratio of these two values, no significant change of $k_{\text{Al.,E}}$ was observed. Based on these calculations, the value calculated from Monte Carlo was used to determine the dose to water from alanine measurement using equation (1), and the type B standard uncertainty of $k_{\text{Al.,E}}$ was estimated to be 0.4%, the difference to the consensus value.

As $k_{\text{Al.,E}}$ was obtained by simulating the dose to alanine in a geometry that reproduced the setup used in the laboratory, including the PMMA sleeve and the presence of seven other pellets, two other conversion factors were calculated, one without the PMMA sleeve and one where only a single centred alanine pellet is simulated. These simulations were done with the aim of evaluating the impact of both the PMMA sleeve and the surrounding alanine pellets. The PMMA sleeve was found to increase the conversion factor by 0.19(14)%.

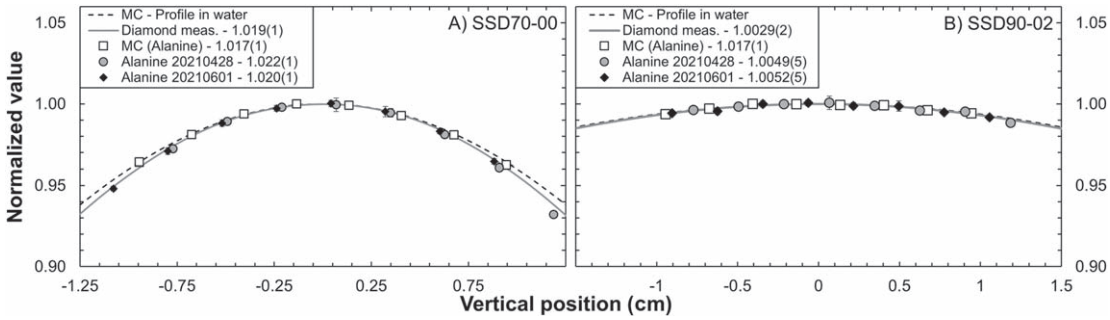

Figure 1. The PTB UHPDR electron beam vertical profile simulated by Monte Carlo in a water scoring volume (black dashed line, uncertainties not shown, ±0.4%) and in an alanine pellets scoring volume (square) compared to the vertical profile measured with a diamond detector (grey solid line, uncertainties not shown, ±0.2%) and the relative measurement in the eight alanine pellets (grey circles for the measurements performed in April and black diamonds for the measurement performed in June). In (A) for the SSD70–00 setup and (B) for the SSD90–02 setup. The numbers indicated in the legend are the values estimated for the vertical field correction factor, $k_{field,v}$.

Table 1. The vertical field correction factor, $k_{field,v}$, obtained by measurement (alanine and diamond detector prototype) and simulated by Monte Carlo.

Setup	Alanine	Diamond detector	Monte Carlo
SSD70–00	1.021(1)	1.019(1)	1.017(1)
SSD90–02	1.0050(5)	1.0029(2)	1.0030(5)

However, the presence of additional pellets has the opposite effect with a similar magnitude. This means that the conversion factor value obtained for a single alanine pellet was found to be the same as for the PMMA-alanine assembly, with a difference of 0.03(14)%. The results obtained for the SSD90–02 beam setup were all within the stated standard uncertainty of values found with the SSD70–00 setup, with a difference of 0.12(14)%.

The measured vertical field correction factor, $k_{\mathrm{field,v}}$, obtained from the relative measurement of the eight alanine pellets irradiated was compared to values obtained from Monte Carlo simulation and estimated from diamond detector vertical dose profile measurements. The results are shown in the table 1.

The vertical beam profiles simulated with Monte Carlo and measured with alanine pellets and diamond detector are shown in figure 1. The obtained correction factors are sensitive to the vertical beam profile shape. This would explain the difference between the values obtained from Monte Carlo simulation and those from measurements, as the simulated beam profile is about 2 mm larger for the SSD70–00 beam setup. The correction factor used is the one obtained from the relative alanine measurement, and a 0.15% type B standard uncertainty was added to the combined relative standard uncertainty as shown in table 2.

The horizontal field correction factor, $k_{\mathrm{field,h}}$, accounts for the horizontal position of the alanine, which is not perfectly centred in the beam since the laser system used to align the PMMA sleeve does not match, within 3 mm, the beam centre. This correction factor was obtained using Monte Carlo simulation as the ratio between the doses deposited in the alanine pellet (1) centred in the beam, and (2) translated by the expected offset between the laser and the beam centre position. As the lateral dose profile in the SSD90–00 beam setup is close to uniformity, the $k_{\mathrm{field,h}}$ correction factor deviates from 1.0 only negligibly. For the SSD70–00, a correction factor based on the relative measurements performed with the diamond detector prototype was estimated and compared with the Monte Carlo simulated value. The $k_{\mathrm{field,h}}$ correction factors were found to be between 1.0000 (7) and 1.0021(7), depending on the slit width, as the beam centre moves by about 1.0 mm in the range of slit widths used. The values estimated from Monte Carlo and relative diamond detector measurements were mutually consistent within the standard deviation. A type B standard uncertainty of 0.15% was assigned to $k_{\mathrm{field,h}}$ as shown in table 2.

3.2. Absorbed-dose-to-water measurement

The relation between the absorbed dose to water measured by means of alanine and the charge measurement of the electron pulses using the ICT are presented in figure 2. The relative residuals of the fitting equation are presented in the lower panels of figures 2(B) and (D). The black dashed line represents the uncorrelated relative standard uncertainty, 0.56%, between the alanine absorbed-dose-to-water measurements performed on different days, i.e. the relative standard uncertainty calculated in table 2 without the uncertainty associated with

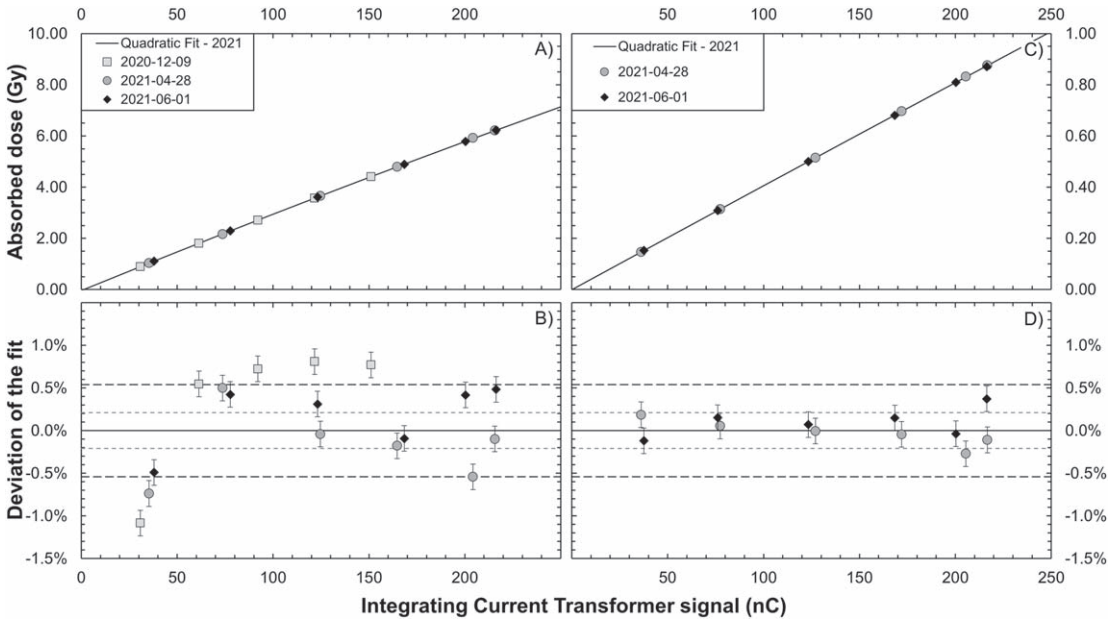

Figure 2. ICT calibration through alanine absorbed-dose-to-water measurement. The results with the SSD70–00 electron beam setup are presented in (A) and (B). The quadratic fit was performed over the measurement between April and June 2021. The deviation between the fit and the measurements is presented in (B). The results of the calibration for the SSD90–02 electron beam setup are presented in (C) and (D). The dashed black line represents the uncorrelated relative standard uncertainty for alanine measurements performed on different days, while the grey short-dashed line represents the uncorrelated relative standard uncertainty within one measurement day.

Table 2. Alanine conversion and correction factor relative standard uncertainty of the absolute-dose-to-water measurement in the UHPDR electron beams at PTB.

	Values source used	Type A (%)	Type B (%)
A_{det}	ESR measurement	0.10[a]	
$\mathscr{A}_{D,w}^{^{60}\mathrm{Co}}$	^{60}Co dose measurement		0.50[b]
k_T	$k_T = 1 - 1.9 \cdot 10^{-3} \cdot (T - 293.15)$	0.04[b]	
m_{det}	Measured mass of pellet	0.04[b]	
$k_{\mathrm{Al.,E}}$	Monte Carlo calculation; 1.010		0.40
$k_{\mathrm{field,v}}$	From alanine measurement		0.15
$k_{\mathrm{field,h}}$	From Monte Carlo simulation		0.15
	Combined relative standard uncertainty		0.68%

[a] Notes. Type A standard uncertainty is obtained by comparing the relative measurement of the eight pellets for the six dose-per-pulse levels measured in each beam setup.

[b] From Anton (2006).

$k_{\mathrm{Al.,E}}$. The grey short-dashed line represents the uncorrelated relative standard uncertainty, 0.24%, between the alanine absorbed-dose-to-water measurements performed with the same reference cobalt pellets used to obtain the dose-normalized amplitude, $\mathscr{A}_{D,w}^{^{60}\mathrm{Co}}$.

The results obtained with the SSD70–00 electron beam setup are presented in the left panel of figure 2. A quadratic fitting equation was selected since the linear fit did not depict the observed measurement trend as expected. The largest deviation from a linear fit was observed for the smallest and largest dose-per-pulse measurement points and was determined to be as much as 2.5% and 0.9%, respectively. As mentioned in the Material and methods section, this observation was expected given that the divergence of the beam is known to change (Bourgouin *et al* 2022). This directly affects the expected linear relationship between the in-beamline charge measurement (i.e. the ICT signal) and the absorbed dose per pulse in the centre of the beam at z_{ref} depth. The measurement results with the SSD90–02 beam setup are presented in the right-hand panels of figure 2. The largest deviation from a linear fit was observed for the smallest dose-per-pulse measurement point and was determined to be 0.35%. A quadratic equation for the fit was also used for reasons of uniformity, although the change in beam divergence has a smaller impact for this beam setup. Based on these measurements, as the relationship between the absorbed dose to water measured by means of alanine is quasi-linear with the number

of electrons accelerated in the beamline, and as the nonlinear behaviour can be explained by a change in the beam divergence, no evidence of dose-response dependency of the PTB's secondary standard system based on alanine was observed.

A beam charge measurement to absorbed dose to water conversion factor was calculated using Monte Carlo simulation for the SSD70–00 electron beam setup. From the simulation, this conversion factor was estimated to be 2.88(3) cGy nC^{-1}. Based on the measurement presented in figure 2, this conversion factor was estimated to be on average 2.92(3) cGy/nC. The difference could be explained by an overestimation of the beam divergence simulated by Monte Carlo. As the beam is not parallel in the beamline and is simulated as a divergent point source, a small overestimation of the beam divergence would explain both a smaller conversion factor and a larger beam lateral profile in water as illustrated in figure 1.

3.3. UHPDR electron beam calibration

As mentioned in the introduction, an alanine dosimeter is not a real-time detector and measurements are time consuming. It is therefore not practical to perform absorbed dose measurement by means of alanine for a range of dose per pulse on a daily or weekly basis while dosimetric investigations are carried out. With this investigation, it was possible to derive a calibration curve for the ICT with the aim of estimating the absorbed dose to water. The following paragraph will discuss the stability and estimated uncertainty of such calibration to determine absorbed dose to water based on in-beamline pulse charge measurement.

For the SSD90–02 beam setup, as shown in figure 2(D), there is no apparent systematic offset due to the use of a quadratic fit to estimate the absorbed dose to water. The average absolute deviation of the quadratic fit to the absorbed dose to water as measured between April and June 2021 is 0.12%. The average absolute deviation of the quadratic fit to the absorbed dose to water as measured between April and June 2021 for the SSD70–00 beam setup is 0.31%. As shown in figure 2(B), the use of a quadratic equation seems to induce a systematic error on the dose estimated for the two lowest calibrations points, around 30 nC and 60 nC. For this reason, an additional correction factor for the ICT calibration was estimated for these two measurement points. The standard relative uncertainty associated with the use of a quadratic fit equation is estimated to be 0.3%. Therefore, the total relative standard uncertainty of the estimated absorbed dose to water from the ICT monitoring system signal is estimated to be 0.75%, the combined uncertainty of absorbed-dose-to-water measurement using alanine dosimeter and the use of a quadratic fit equation.

The quadratic fit calculated from the absorbed-dose-to-water measurement compared to the pulse charge measurement obtained between April and June 2021 for the SSD70–00 beam setup were compared to a calibration performed in December 2020. As shown in figure 2(B), the results of December 2020 are not within the uncorrelated relative standard uncertainty for alanine measurement of 0.56%. The December 2020 calibration was performed using slightly different linac parameter settings. Some preliminary measurements have shown that these parameters could impact the signal by up to 4%. As shown in figure 2(B), the results of April and June 2021 agree within the standard uncertainty. These results indicated that a pulse charge to absorbed dose calibration curve would be adequate for dosimetric investigation over several months, provided the linac settings and output remain unchanged.

To evaluate the performance of the calibration curve of both electron beam setups, the diamond detector prototype measurement was used to compare the calibration of the ICT for both reference electron beam setups. Since there is only a slight gap between the dose-per-pulse ranges of the two beams, the two beam setups can be compared to see if any systematic offset exists, something that would be indicated by a significant discontinuity between the two measurement ranges. The dependence between the diamond detector signal and the measured absorbed dose to water per pulse is presented in figure 3(A).

The diamond detector prototype is known to be linear over a large range of dose per pulse, but nonlinear behaviour is expected in the highest dose range, $>$2.5 Gy per pulse (Kranzer *et al* 2022). Therefore, the linear fit presented in figure 3(A) and used to obtain the residuum presented in figure 3(B) is calculated from a dose-per-pulse range of 0.1–2.3 Gy, which combines values from both electron beam setups. As shown in figure 3(A), the diamond detector prototype shows linear behaviour for signals up to 1.55 nA, equivalent to an instantaneous dose rate of about 1 Gy μs^{-1}.

The dashed horizontal line in figure 3(B) is the uncorrelated relative standard uncertainty between the two beam setups for absorbed dose to water obtained using the ICT calibration. This uncertainty was determined to be 0.38% since the uncertainty associated with the alanine reference cobalt pellets and $k_{Al.,E}$ should not be included in the calculation of this uncertainty. In figure 3(B), it can be observed that the value obtained for a dose slightly higher than 1 Gy, i.e. the lowest dose per pulse with the SSD70–00 beam setup, is larger than the linear fit by 0.52(1)%, which is slightly greater than the estimated uncorrelated relative standard uncertainty. These results indicated that the relative uncertainty associated with the use of a calibration curve should be increase to

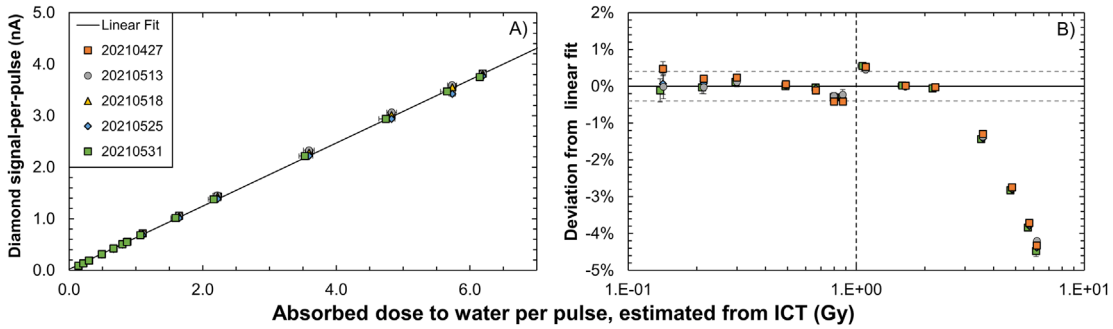

Figure 3. Diamond detector prototype signal versus the estimated absorbed dose to water from ICT calibration in (A). The values presented are the average for a week of measurement and the error bar represents the standard deviation observed. The linear fit is done for a range from 0 Gy to 2 Gy per pulse for each week separately. The deviation from the linear fit is presented in (B). The horizontal dashed line is the uncorrelated relative standard uncertainty between the two beam setups for absorbed dose to water obtained using the ICT calibration and the vertical line represents the delimitation between the two electron beam setups.

0.5%. The large deviation observed, up to −5%, for doses per pulse higher than about 2.5 Gy, is due to the nonlinear dose response of the diamond detector (Kranzer *et al* 2022).

4. Conclusion

The aim of the presented study was to evaluate the dose response of the alanine and ESR system as a secondary standard in UHPDR electron beams. The different field correction factors as well as the beam quality conversion factor to account for the different dose response in the calibration ^{60}Co beam and the electron beam were obtained using Monte Carlo simulations. The field correction factor was also compared with a value determined experimentally from lateral beam profile measurements using a diamond detector prototype. The beam quality conversion factors, $k_{\mathrm{Al.,E}}$, obtained from Monte Carlo simulations were found to be consistent within the standard uncertainty for both reference electron beam setups, SSD70–00 and SSD90–02. The obtained value, 1.010(1), is within the standard deviation of the consensus value of 1.014(5) (McEwen *et al* 2020).

The absorbed dose to water determined using alanine was evaluated for a range of dose per pulse from 0.15 Gy to 6.2 Gy. The combined relative standard uncertainty was determined to be 0.68%, which is close to the value obtained in a conventional dose rate beam (McEwen *et al* 2015). The relationship between the obtained dose per pulse and the in-beamline pulse charge measurements with a non-destructive integrating current transformer (ICT) was evaluated. The absorbed dose to water determined by alanine measurements showed a quasi-linear behaviour with respect to the number of electrons accelerated, the ICT signal. The nonlinear relationship between the absorbed dose measured at the reference depth and the pulse charge was explained by the change in the beam divergence when the slit width was adjusted to change the dose per pulse. From these measurements, it can be concluded that no evidence was found of a dependence of the dose response of the alanine/ESR secondary standard dosimetry system at PTB on the instantaneous dose rate.

In this investigation, a calibration curve based on a quadratic equation for the ICT was determined in the aim of estimating the absorbed dose to water. The performance of the obtained calibration curves for both reference beams, SSD90–02 and SSD90–00, was evaluated using a diamond detector prototype. The maximum deviation from linearity observed using the diamond detector prototype (within the linear response range of the detector), was evaluated to be 0.52%. This observation indicated that the combined uncertainty of the absorbed dose to water estimated from the calibration curve should be increased to 0.85%, the combined uncertainty of absorbed-dose-to-water measurement using alanine dosimeter (0.68%) and the use of a quadratic fit equation (0.5%).

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Conflict of interest

Rafael Kranzer is an employee of PTW Freiburg. Marco Marinelli signed a contract with PTW Freiburg involving financial interests deriving from the commercialization of the PTW microDiamond 60019 dosimeter. The remaining authors declare that their research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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