A framework for $e^+e^-$ annihilation detection using nano-particles for tumour targeting in radiotherapy

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Abstract. The quality of modern patient radiotherapy treatment is strongly dependent on reliable and accurate dosimetry techniques. Although desirable, in situ and in vivo dosimetry is usually hard to implement in routine radiotherapy procedures. The potential use of nanoparticles has been recently considered for biomedical applications achieving promising performance for diagnosis as well as therapeutic practices. The present work reports about a novel proposal based on the use of high atomic number nanoparticles for online estimation of absorbed dose during conventional radiotherapy treatment. In this first phase, the investigation handles with experimental and theoretical tasks regarding the potential use of the variations in the annihilation peak and its correlation with the presence of high atomic number nanoparticles acting as signal enhancers. Dedicated Monte Carlo simulations are also presented in order to complement experimental results and theoretical models. Although the correlation between annihilation peak with the presence of nanoparticles was successfully confirmed, further investigations are still necessary in order to estimate feasible absorbed dose from determinations of annihilation peaks.

1. Introduction

Imaging and therapeutic techniques aimed to deal with neoplastic diseases incorporate the use of ionizing radiation as part of the medical procedure. In this context, it is crucial to achieve reliable and accurate dosimetry. This task can be addressed by experimental methods for in-vivo or in-phantom dosimetry, as well as calculations based on models for radiation transport in biological systems. It may be desirable to develop methods capable of in situ and online dosimetry. However, it is difficult to find worldwide established commercial techniques available for this purpose. Significant efforts are currently dedicated to the study of novel methods with such capabilities. During the last years, the potential use of nano-particles (NPs) in radiation oncology applications was largely investigated.
focusing the attention of radiology and treatment improvement by radio-sensitivity enhancement[1,2]. High atomic number (Z) NPs are becoming one of the most promising contrast agents for computed tomography (CT) due to their remarkable properties including high X-ray absorption coefficient, tailored surface chemistry, and excellent biocompatibility[3]. Thus, the increased photoelectric absorption probability produces an increased absorbed dose close around the target site minimizing harmful radiation to normal tissues. Although iodine was the first element investigated to enhance local tumor control by using high Z materials[4], gold NPs appear nowadays probably as the most promising technique to this aim[5,6]. Gold NPs have also the due to strong NIR light absorption, the majority of interest in potential for photo-thermal cancer therapy due to the large amount of heat generated by near infrared (NIR) irradiation[6]. On the other hand, the principle of contrast enhancement by high Z agents is based on the fact that high Z materials present, normally, higher physical density than most of the atoms in biological tissues. Current radiology techniques are mainly based on absorption contrast imaging, therefore the more efficient X-ray absorption of high Z materials leads to the improvements in radiology image contrast[2,4].

It is well known that when using X-rays with energy around 100 keV, the presence of high Z NPs produces the emission of characteristic fluorescent lines than can be accurately detected[7,8]. However, during typical radiotherapy treatments, the irradiation beams have significant higher energies according to accelerating voltages around 6-18 MV. Clinical implementation of radiology techniques based on NPs detection, and associated potentiality for tumor localization and radio-sensitivity enhancement requires specific investigations of such processes for megavoltage photon beams. Therefore, the annihilation peak, that is dependent on irradiated material properties, might appear as a suitable parameter to be investigated to this aim. This work reports on preliminary results regarding the design and experimental setup to determine the feasibility and reliability of using prompt gamma emission from positron-electron (e^+\text{--}e^-) annihilation as qualitative/quantitative correlated parameter for detecting the presence and localization of high Z NPs within biological tissues and, eventually, to establish a correlation with local absorbed dose. The first step consisted of modeling the effect on the radiation-matter interaction properties by means of calculating effective macroscopic cross sections according to the actual concentration of NPs within the water-equivalent phantoms that reasonably mimic low Z biological tissues for radiology purposes. Special interest was dedicated to the theoretical calculation of e^+-e^- pair production-annihilation. Additionally, Monte Carlo (MC) subroutines were developed in order to perform simulations to investigate both, radiation production and further detection processes with the aim of seeking for correlations between e^+-e^- annihilation photon emissions with the type, spatial distribution and concentration of the NPs.

2. Materials and Methods

This section reports about theoretical approaches, as well as experimental and virtual (Monte Carlo) methodologies for radiation-matter interactions within systems consisting of small fractions of high Z NPs diluted in low Z and quite water equivalent media.

2.1. Models for pair (e^-e^+) production and annihilation for systems of NPs in biological tissues

The pair production-annihilation processes are already well described in literature[9, 10], therefore only a brief summary is presented in this Section providing the main issues about the underlying physics for e^-e^+ production and associated annihilation photons.

The e^+-e^- pair production concerns a transition between an initial state comprehended by two photons of different origin, and a final state corresponding to a positron and an electron. One of the
photons is generated in the laboratory frame, possibly by Bremsstrahlung, and must have a total energy \( E_\gamma \) satisfying \( E_\gamma \geq 2m_0c^2=1.022 \text{ keV} \), where \( m_0 \) is the electron rest mass and \( c \) is the speed of light in vacuum. The other photon comes from the Coulomb field of another particle such as an atomic electron or the nucleus. For the purposes of the present work, the theoretical approach is based on the fact that the pair production is due to the nuclear Coulomb field, as sketched in the laboratory reference system in figure 1.

![Figure 1: Sketch of e⁻-e⁺ pair production in the laboratory inertial system due to a Z atomic number nucleus.](image)

Determination of the microscopic cross section for e⁻-e⁺ pair production in nuclear Coulomb field is a canonical problem that can be solved in the first Born approximation as proposed by Bethe and Heitler[11]. The result is stated as a three differential cross section on positron energy \( \alpha \) dependence on positron energy \( E_\gamma \) and momentum angles \( \theta_\gamma \). Then, introducing the unit system \( \hbar = c = 1 \), it results for electron and positron momenta:

\[
\frac{d\sigma}{dE_{\gamma}} \propto \frac{\rho^2 \rho' \frac{dE_{\gamma} \partial^3 \partial \gamma}{\partial \rho^0 \partial \rho'} \Theta(E_{\gamma} - E_{\gamma} - m_0) \ F(p_{\gamma}, \ p_{\gamma}'; \ k_{\gamma}'), \ (1)
\]

where \( \alpha \) is the fine structure constant, the \( F \) function depends on the 4-momentum of the three particles[12] and \( |q| \) is the magnitude of the 3-momentum transferred to the nucleus, while the Heaviside step function \( \Theta \) ensures a zero value for the cross section if \( E_{\gamma} - K_\gamma < 2m_0c^2 \), i.e. the threshold for pair production. Although this approach for the cross section does not account for the electron cloud screening or the internal structure of the nucleus, it may be useful to integrate expression (1) with respect to angular variables \( \Omega_\gamma \) in order to assess an approximation for the dependence on positron energy \( E_{\gamma} \), as reported in figure 2.

![Figure 2: Theoretical approach for the microscopic cross section for e⁻-e⁺ pair production in Au (Z=79) as a function of positron energy \( E_\gamma \) for different \( E_\gamma \) photon energies.](image)
Similarly, fixing the positron energy $E_+$ to the most probable case, *i.e.* half the photon available energy, formula (1) can be plotted as a function of both, positron and electron angles ($\theta_+\gamma$ and $\theta_-$, respectively) as shown in Figure 3.

![Figure 3: $e^-e^+$ pair production microscopic cross section as a function of the scattering angles $\theta_+$ and $\theta_-$ considering symmetric distribution of incident photon energy.](image)

This result is useful to predict the most probable directions for the creation of the $e^-e^+$ pair, which correspond to the forward direction according to the incident $\gamma$ photon. As expected, the angle corresponding to the maximum in this surface ($\theta_\gamma$) is symmetrical for the $e^-e^+$ pair having the value $\theta_\gamma = 12.6^\circ$ (0.2199 rad). As for the energy, the positron angle should be slightly greater because of the Coulomb repulsion with the nucleus, but the effect was neglected in this approach.

The proposed approach to investigate the macroscopic cross sections for systems consisting of high Z NPs in biological soft tissues is based on some assumptions: the mixture can be modeled, for radiology purposes, as being composed of a low percentage (weight in weight, w/w) of high Z NPs diluted in water equivalent media, therefore constituting a homogeneous soup of atoms, as usually treated by Monte Carlo techniques. However, for other physicochemical purposes, it may be necessary to take into account that NPs are in a solid phase suspended in liquid buffer.

According to the aim of the present work, it is necessary to estimate the effective macroscopic cross section for systems consisting of high Z NPs diluted in liquid water, which are irradiated by high energy (6 MV) photon beams used for radiotherapy. Specifically, it is required to know the influence on the effective macroscopic cross section due to NPs type and concentration. The spectrum of the incident photon beam corresponds to the Varian 610C linear accelerator (linac) is available in literature [14] and it is shown in Figure 4.
The effective macroscopic cross sections, weighted over photon spectrum, were calculated based on data provided by NIST database about cross sections for pure elements and some specific compounds, like liquid water. For the purposes of the present work, regarding radiology properties of high Z NPs, the proposed approach consists on estimating the compound cross section in terms of pure element cross sections according to Bragg’s additivity rule[15, 16]. If \( \sigma_i \) is the cross section of \( i \)-th element, and \( N_i \) is the number of atoms of that element present in the compound, then the total cross section \( \sigma \) for the compound can be approached as:

\[
\sigma \approx \sum_i N_i \sigma_i.
\] 

Therefore, in the framework of the proposed approach, the effective cross section \( \sigma_{\text{eff}} \) can be estimated for the corresponding photon beam by means of a proper weighted average over photon spectrum (\( \phi(E) \)) and NPs concentration (\( x \% \text{ w/w} \)):

\[
\sigma_{\text{eff}} \approx \frac{\int dE \sigma_i(x \% \text{ w/w}) \phi(E)}{\int dE \phi(E)}.
\] 

This formalism was applied to estimated effective cross sections (pair production and total) for systems containing different concentrations (w/w) of NPs of Ag, Gd and Au, as summarized in figures 5 and 6.
As reported in Figures 5 and 6, it is verified that the effective pair production cross section increases according to NPs concentration, and this effect is greater for higher Z NPs. Hence, the probability of producing a pair and associated annihilation photons is increased in terms of NPs atomic number and concentration. This characteristic stands as a key issue and primary motivation for the present work.

2.2. Experimental setup for NPs detection during radiotherapy irradiation

Experimental setup was designed and implemented in bunker facility with a Varian Clinac 610C linac dedicated to routine clinical use for patient treatment. As mentioned, the linac works delivering a 6 MV photon beam that can be adjusted to different dose rates according to the required monitor units (MU) value determined in monitor ionization chamber. Field size, source-to-surface distance, incident direction and other irradiation parameters were configured according to the purposes of the different objectives of the present work. The detection system consists of a Canberra high energy germanium detector model GL1010 based on semiconductor diodes having a P-I-N structure with intrinsic region (I) sensitive to ionizing radiation, particularly X- and γ-rays. The operating principle of this kind of detectors are widely described in literature, then only a brief description about its main issues is presented. Incident photons interact with the material within the depleted volume of a detector producing charge carriers (holes and electrons) that are swept by the electric field to the P and N electrodes. This charge, which is in proportion to the energy deposited in the detector by the incoming photon, is converted into a voltage pulse by an integral charge-sensitive preamplifier. Because germanium has a relatively low band gap, this type of detectors requires to be cooled to reduce the thermal generation of charge carriers (thus reverse leakage current) to an acceptable level. Otherwise, leakage current induced noise destroys the energy resolution of the detector. Liquid nitrogen is the commonly recommended to be used for cooling purposes in such detectors, as followed in the present work. The GL1010 detector operates with the digital pulse processor (DPP) AMPTEK® model HPGe-PX5. The PX5 replaces both the shaping amplifier and multi-channel analyzer (MCA) found in analogue systems and it is capable of controlling the preamplifier output, applying real-time digital processing to the signal, detecting the peak amplitude, and binning this in its histogram memory. The spectrum is then transmitted to the user’s computer. Actually, PX5-HPGe is a modified version of PX5 signal processor and power supply. A custom power supply board is installed in a standard PX5, providing the higher bias voltages needed by a germanium detector along with the higher pre-amplified power voltages and currents required by most preamplifiers. This DPP includes dedicated software (DPPMCA) capable of changing acquisition parameters such as coarse and fine

![Figure 6: Pair production effective cross section for different NPs types.](image)
gain, low and high thresholds of the respective slow and fast channels of pulse processing, number of channels in the spectrum, energy range calibration, among others.

Different phantoms were used for experimental measurements in form of cylinders made of cellulose ($\text{H}_\text{n}\text{C}_\text{o}\text{O}_\text{y}$) and having $(3.2\pm0.1)$ cm and $(2.6\pm0.1)$ cm in diameter ($d$) and height ($h$), respectively. The mass was determined to be $m = (20.23 \pm 0.01)$ g and the mass density was estimated as $\rho = (0.97\pm0.7)$ g cm$^{-3}$. One of the phantoms has a small cavity were plastic vials with NPs-buffer are located, whereas the second one is absolutely solid.

The gold NPs used in the present work were provided by AuroVist$^\text{TM}$ certifying 15 nm as dimension distribution of the Gold BloodPool X-ray Contrast Agent distributed in nano-probes. Silver nano-particles are made at home, following the protocol described elsewhere$[8]$ with dimensions characterized by size distributions with 15 nm as mean diameter. A vial was prepared with this Au NPs diluted in a buffer consisting of 20 mM of sodium phosphate and 150 mM of sodium chloride (NaCl). The sodium phosphate is a mixture of monobasic sodium phosphate ($\text{Na}_2\text{HPO}_4$) and dibasic sodium phosphate ($\text{NaH}_2\text{PO}_4$).

The setup for the experiments was previously investigated by analytic and Monte Carlo approaches. A sketch of the experimental disposition of irradiation source, phantoms, and collimation and detection systems is presented in figure 7.

![Figure 7: Experimental setup including phantom with NPs (red cylinder) and collimation system (3 sets of lead shutters). Ge detector (not shown) was placed at all positions immediately before and after shutters, as indicated in black lines.](image)

The incident photon beam was set to $3.5\times3.5$ cm$^2$ field size placing the center of the phantom at the linac isocenter with the gantry at $180^\circ$. The collimation aperture of each shutter was carefully investigated in order to establish the optimal configuration providing good enough signal-to-noise ratio for the annihilation peak but avoiding saturation and maintaining appropriate detection dead times (lower than 5%). Nevertheless, an extra 1mm diameter Pb collimator is attached at the Ge entrance window in order to avoid lateral scattering contributions. In this framework, detection was realized at $90^\circ$ respect the incidence photon beam performing, in all cases, two separate set of measurements: homogeneous cellulose phantom and cellulose phantom containing vial with NPs.

Finally, once photon spectra are recorded by Ge detector, the proposed procedure consists of performing offset correction and channel-energy calibration, and after that, for comparison purposes, the corresponding spectra processed according to the following formalism: The recorded and corrected signal $\Phi$ is then normalized by means of:
Monte Carlo simulations for NPs detection and dosimetry purposes

Monte Carlo simulations are nowadays one of the most useful and frequently used techniques for particle interaction and radiation transport modelling. Applications of Monte Carlo methods for medical physics purposes have grown systematically during the last decades mainly due to advances in computation technology. FLUKA[17] and MCNP6[18] main codes were used for the purposes of the present work. FLUKA main code is a general purpose Monte Carlo simulation package that fully integrates particle physics being capable of dealing not only with electron and photon transport, but also with complete models along with crosstalk for all radiation components with particular interest on heavy ions. FLUKA uses a multiple scattering approach for charged particle transport implementing a dedicated algorithm based on Molière’s theory. The lowest transport limit is 0.1 keV for photons and 1 keV for electrons. Multiple scattering is implemented by Molière models providing also single scattering options that may be useful for low energy ranges. MCNP6 is a general purpose, continuous-energy, generalized-geometry and time-dependent Monte Carlo radiation transport code, designed to track particles of many types and broad ranges of energies. Contrary to previous versions, MCNP6 has been expanded to handle a multitude of particles and physical models improving transport and tracking issues. According to the aim of the present work, both Monte Carlo codes are capable of satisfactory handle incoherent and coherent scattering, fluorescent emission after photoelectric absorption, Bremsstrahlung and absorption in pair production with local emission of annihilation radiation.

Simulation setup for FLUKA and MCNP codes were prepared exactly according to disposition shown in figure 7. The inputs for the simulation subroutines define the incident photon beam 3.5×3.5 cm² with spectrum according to Figure 6. Tallies were introduced to compute photon fluence at different positions where the Ge detector was placed in experimental measurements, as shown in figure 7. Simulations were performed for 5×10⁹ primary particles with absorption energy thresholds set to 50 keV for both photons and electrons, thus requiring 72 and 120 hours for FLUKA and MCNP6, respectively.

In addition to the calculations dedicated to simulate experimental setup including the NPs, other Monte Carlo simulations were prepared aimed to validate the theoretical approach proposed to model cross sections of systems consisting low percentages (weight in weight) of high Z NPs diluted in low Z buffers. In these cases, the geometrical setup consists on a thin layer irradiated by a mono-directional beam and transmitted/scattered radiation is recorded by impact detectors at different positions as shown in figure 8.

\[
\Phi_{Norm}(E) = \frac{\Phi(E)}{\int dE \Phi(E)}
\]
3. Results and Discussion

The first step consisted on investigating the performance of the proposed theoretical approach to model radiation-matter interaction in systems composed by low percentage (w/w) of high Z NPs diluted in water-equivalent media. This goal was accomplished by means of evaluation and comparison of Monte Carlo simulations carried out by different and independent validated Monte Carlo codes, FLUKA and MCNP6. As mentioned above, expression (1) can be integrated using the angles in order to get an approximate estimation for the cross section differential in positron energy, as reported in figure 2 for the theoretical approach. The corresponding results for Monte Carlo simulations are shown in figure 9.

In order to contrast the theoretical predictions on pair production, simulation of an Au foil of $\Delta z = 0.01$ cm of thickness was performed the FLUKA code using a photon pencil beam with energy equivalent
to the effective energy [19] of the linac spectrum of Figure 6 (2.2 MeV), so that the energy expected for the positrons is in the range $0 \leq K_e \leq 2.2 \text{ MeV} - 2m_0c^2 = 1.18 \text{ MeV}$.

As can be seen by inspection of Figures 2 and 11, neglecting nuclear Coulomb field yields slightly more energy to the positron due to repulsion, thus making the cross section symmetrical respect to $K_e = -2m_0c^2$. The difference of energy delivered to the photon taking into account the Coulomb repulsion is always less than $\delta(E) = 0.0075 \cdot Z \text{ MeV}$ [20]. As obtained in figures 2 and 9, both the extreme cases when the positron takes all available energy from the photon, or it takes any, have zero probability of happening. Complete positron current leaving the foil was calculated. These relative energy distributions were normalized to the maximum value of the theoretical distribution at $\frac{K_e}{E_\gamma - 2m_0c^2} = \frac{1}{2}$ that explains why the simulated energy distribution is asymmetrical respect to this point, showing that FLUKA code includes actually an adequate treatment of the nuclear Coulomb repulsion effect over created positrons. Additionally, as the theoretical distribution was calculated in the Born approximation, it tends to fail when photon energy is close to the pair production threshold, or when electron or positron takes all the available energy. This issue corresponds to a failure in the assumptions of point nucleus without Coulomb screening effect due to the electronic cloud for the theoretical calculations. Nevertheless, the energy difference between the maximum of both distributions is $\delta(E) = 0.13 \text{ MeV}$ satisfying the condition: $\delta(E) = 0.13 \text{ MeV} < 0.0075 \cdot Z \text{ MeV} = 0.59 \text{ MeV}$ for Au ($Z=79$).

The angular distribution of positrons calculated through Monte Carlo simulation, reported in Figure 11, was obtained with the half-crown geometry of impact detectors, as shown in figure 8 locating the impact detectors (cylinder 2 cm radius and 1 cm height) were located at 25 cm from the center of the foil. According to the obtained results reported in figure 9, it is possible to observe that: sticking to the most probable cases (available energy uniformly distributed and directions close to the that of the initial photon), FLUKA code makes a good approximation of the pair production phenomena, giving correct energy distributions with fine details as the Coulomb repulsion and electron cloud screening effect. Furthermore, the angular distribution of positrons is shown to have approximately the same behavior predicted theoretically for MC simulations, allowing this tool to model pair production in an accurate way. Finally, and according to the purposes of the present work, it should be mentioned that the $\sim O(Z^2)$ behavior of expression (1) adequately describes the relevant behavior for the effective cross section of systems composed by low percentage (w/w) of high Z NPs, such as Gd, Ag, Au, diluted in water-equivalent media.

Regarding the $e^-e^+$ annihilation, it was confirmed by FLUKA and MCNP6 Monte Carlo simulations with the concentric spheres that maximum of cross section corresponds to directions close to that of the pair in the CMS reference frame. Simulations were performed using the internal sphere ($r_{in} = 0.5$ cm) as emulating the tumor containing 0.1% of Au NPs dilute in water-equivalent tissue; whereas the external sphere ($r_{out} = 1.0$ cm) emulating patient body was made of water-equivalent tissue. Therefore, the tumor is located 0.5 cm depth in water-equivalent material. As sketched in figure 8, the source is positioned in the region inside the half-crown of detectors 14 cm shifted from the center of the phantom. The detected spectra obtained with FLUKA and MCNP6 by means of the quarter-crown detection system are reported in figure 10.
As shown in the results summarized in figure 10, the angular behavior is similar in both Monte Carlo codes and the peak probabilities are almost the same, as can be seen in figure 11.

According to the results reported in Figure 11, angular dependencies show similar trends for FLUKA and MCNP6. Considering that integral of peak counts is approximately constant for different directions, it might be acceptable to place a detector 90° respect initial photons incidence direction in order to achieve the good signal-to-noise ratio (SNR) but making it easier to design and implement the experimental setup.

3.1. Detection of NPs during radiotherapy irradiation by Monte Carlo simulations

The difference of the annihilation peak intensity with and without NPs in the anthropomorphic phantom was calculated using Monte Carlo code FLUKA. The geometry is depicted in figure 7. The input file included an external subroutine defining the source as a 3.5x3.5 cm2 extended field with
energy distributed according to Mohan et al spectrum. The materials for cellulose and buffer plus NPs were defined using the chemical composition already explained. The spectra were measured in the different impact detectors shown in figure 7, but those after the first lead shutter were not able to measure anything even for $10^9$ primary photons. The impact detector that simulates the Ge detector shows zero signal, and thus the first impact detector in the direction of the Ge detector was used for comparison with experimental results. The spectra measured in this case, shows a Dirac’s delta annihilation peak, as can be seen in figure 12.

![Photon spectra estimated with FLUKA MC Code for the anthropomorphic phantom with and without Au NPs](image)

Figure 12: Photon spectra estimated with FLUKA MC Code for the anthropomorphic phantom with and without Au NPs

In this case, using equation (4) with the values at the peak, the intensity of the annihilation signal with NPs is of the order of 2.1% more intense than the peak without NPs.

3.2. Experimental detection of NPs during radiotherapy treatment

As described above, the experimental setup, preliminary validated by Monte Carlo simulations, was designed and configured exactly according to the simulations, as sketched in figure 7 using the linac couch was used as bench top for the positioning of the different accessories: phantoms, collimation systems and detectors. Figure 13 shows a typical example of the spectra recorded by the Ge detector for Au NPs. Contrary to Monte Carlo simulation, a spread annihilation peak was obtained in every measurement due to the intrinsic limitation of experimental detector to discriminate photons with similar energies, thus assigning the count to adjacent channels in the spectrum.
The annihilation peak intensity in the case of cellulose phantom doped with Au NPs is, in average, 1.73\% more intense than the case without NPs. Even though this tendency is marked, this difference is smaller than the percentage experimental error at the annihilation peak, that is 3.5\%, thus being indistinguishable.

4. Conclusions

A theoretical approach was proposed and implemented to model and preliminary estimate cross sections of systems composed by water with low quantity of high atomic number nanoparticles diluted within it. Dedicated Monte Carlo subroutines were adapted to investigated basic radiation-interaction process for this kind of systems obtaining very good agreements with theoretical predictions.

Moreover, experimental setups were carefully designed and investigated in the virtual environment of Monte Carlo simulations using to independent Monte Carlo codes. Finally, it was possible to perform complex and high demanding experimental measurements that confirmed variations in annihilation peak due to the presence of nanoparticles during standard irradiation with photon beam from linear accelerator for patient treatment.

Although the obtained results appear as promising for establishing a preliminary framework for theoretical, simulation and experimental approaches to study these processes, further investigations are still necessary in order to achieve definitive and conclusive evidence and correlation between annihilation peak variations, nanoparticle presence/concentration and, potentially, absorbed dose during patient radiotherapy treatments.
5. References

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