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REVIEW ARTICLE

Clinical applications of alanine/electron spin resonance dosimetry

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Abstract This paper discusses the clinical applications of electron spin resonance (ESR) dosimetry focusing on the ESR/alanine system. A review of few past studies in this area is presented offering a critical overview of the challenges and opportunities for extending this system into clinical applications. Alanine/ESR dosimetry fulfills many of the required properties for several clinical applications such as water-equivalent composition, independence of the sensitivity for the energy range used in therapy and high precision. Improvements in sensitivity and the development of minidosimeters coupled with the use of a spectrometer of higher microwave frequency expanded the possibilities for clinical applications to the new modalities of radiotherapy (intensity-modulated radiation therapy and radiosurgery) and to the detection of low doses such as those present in some radiological image procedures.

Keywords Alanine · Electron spin resonance · Electron paramagnetic resonance · Dosimetry · Clinical applications

Introduction

In radiation therapy, the dose delivered to the tumor and its distribution in the surroundings is of critical importance, since both the probability of tumor control and normal tissue complications show a steep sigmoidal relationship with absorbed dose (Schaeken and Scalliet 1996; Wielopolsi et al. 1987). Taking into account the positioning of the dosimeter in the region of interest, the alanine/ESR dosimetry system [ESR stands for electron spin resonance and other names refer to the same technique as electron paramagnetic resonance (EPR) and, more recently, electron magnetic resonance] represents a very suitable method because it is tissue equivalent, for beam energies used in therapy, so it does not cause disturbances or discontinuities in the volume in which the system is present. In addition, it provides further characteristics that will be discussed here, which are essential for medical applications (Regulla and Deffner 1982).

Alanine (2-aminopropanoic acid) is the smallest and simplest amino acid participant of molecular biosynthesis. Its molecular structure $CH_3CH(NH_2)COOH$ consists of a carboxylic group (COOH), amino (NH_2) group, a methyl (CH_3) and a hydrogen atom all bound to a central carbon atom. The methyl group is responsible for differentiating alanine from other amino acids. It exists in two isomeric forms: L- and D-alanine, and a racemic mixture of them results in the DL-alanine form. The L- and DL-alanine are the most common forms used for dosimetry (Fig. 1).

The interaction of ionizing radiation with alanine triggers a series of reactions giving rise to radicals. The most stable corresponds to the breaking of the NH_2 group bound (Heydari et al. 2002; Miyagawa and Gordy 1960). Thus, the presence of an unpaired electron with the central carbon assigns paramagnetic properties and is responsible for the central line of the spectrum, as shown in Fig. 2. The adjacent lines are due to hyperfine interactions of the unpaired electron with the four hydrogen atoms present in the radical CH_3–C·H–COO. Therefore, the characteristic ESR spectrum of irradiated alanine consists of a central

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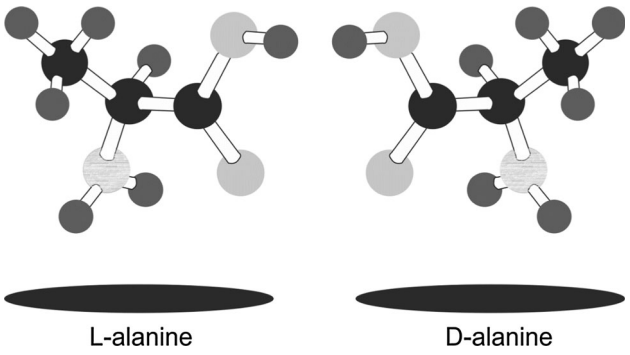

Fig. 1 Molecular structure of L-alanine and D-alanine. Carbon (*black*), hydrogen (*gray*), oxygen (*light gray*) and nitrogen (*shadow light gray*). The L isomer has a higher ESR signal than the D isomer

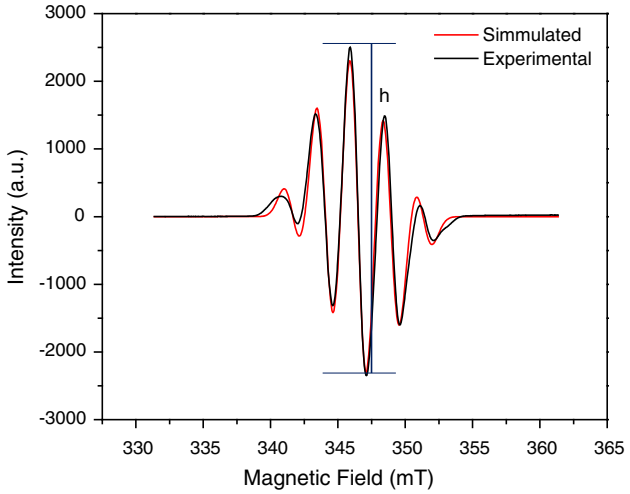

Fig. 2 Experimental and simulated ESR spectra of L-alanine irradiated with a dose of 150 Gy of ^{60}Co showing the *central line* and hyperfine interaction. The amplitude h is used for the *calibration curve*. The experimental spectrum was recorded by means of a JEOL FA-200 X-band spectrometer, and simulation was performed using WinEPR Simfonia (Bruker)

line of greater amplitude and four sidelines with smaller intensity.

Thus, the number of paramagnetic centers created by ionizing radiation can be detected by an ESR spectrum. The ESR/alanine dosimetry is based on the determination of the concentration of unpaired electrons produced by the interaction with ionizing radiation (Miyagawa and Gordy 1960). It consists of recording the ESR spectrum (usually the first harmonic signal or the first derivative of the absorption line) of irradiated alanine (Fig. 2) under certain experimental conditions. For purposes of dosimetry, if the modulation amplitude and the microwave power are kept constant in all measurements, the amplitude h of the center line of the spectrum can be directly correlated with the dose, and it is interpreted as the "reading" of the dosimeter

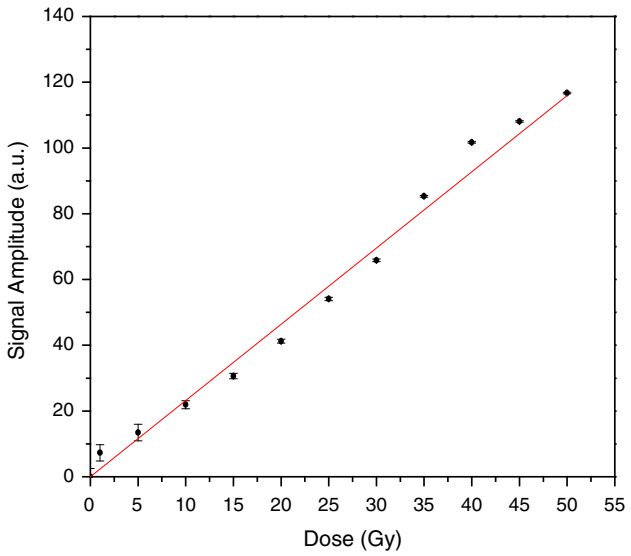

Fig. 3 Dose–response curve (*DRC*) of L-alanine, showing the linear relationship of the amplitude with dose up to 50 Gy

(Regulla and Deffner 1982). For a given dose interval, the variation of h with dose shows a linear relationship, as illustrated in Fig. 3. The linear behavior of the dose–response curve extends from a few Gy to about 100 kGy. Above, the curve is sublinear, achieving a saturation region through a maximum at about 1,000 kGy (Regulla and Deffner 1982). Besides showing this linear behavior in a wide dose range, alanine has other qualities that makes it a suitable dosimetric material, such as a response independent of the radiation energy above 100 keV and independent of dose rate (Borgonove et al. 2007; Regulla and Deffner 1982; Waldeland and Malinen 2011). In the early 1980s, the International Atomic Energy Agency (IAEA) chose alanine, among various other types of dosimeters, and used it in the program of standardization of high-dose measurements due to the following qualities: (a) There is only little decay of the ESR signal with time (temporal stability), (b) alanine dosimeters require no heat or chemical treatment before and after irradiation and (c) the signal is not destroyed after reading or recording of the spectrum, allowing to save dosimeters for posterior reassessment if necessary (Nam and Regulla 1989). In addition, alanine also shows a response to neutrons, protons and ion beams, making it a suitable dosimeter for the new modalities of radiotherapy (Herrmann et al. 2011; Onori et al. 1997; Trompier et al. 2004).

The procedures for using alanine/ESR dosimetry are established in the ISO/ASTM 51607:2013 protocol that describes dosimeter preparation and instrumentation for measurements of absorbed dose in materials irradiated with photons and electrons. The alanine dosimeter may be used either as a reference standard dosimetry system or as a

routine dosimetry system. ISO/ASTM 51607:2013 is one of the sets of standards that provides recommendations for properly implementing dosimetry in radiation processing and describes a means of achieving compliance with the requirements of ASTM E2628 for the alanine dosimetry system.

During the 1980s, after the seminal publication by Regulla and Deffner (1982), the main focus of alanine application was on industrial dosimetry with doses of the order of kGy such as those used in the process of food irradiation and sterilization of medical products (Van Van Laere et al. 1989; McLaughlin and Desrosiers 1995; Wieser and Regulla 1989). With the advent of more sensitive spectrometers, the therapeutic dose range became accessible (Anton et al. 2009; Nagy et al. 2002; Sharpe et al. 1996).

For radiation therapy, a small uncertainty in the measurement of the applied dose is required. Bergstrand et al. 1998 and Anton (2006) discussed the necessary conditions to achieve precision and accuracy with the alanine dosimetric system. The uncertainty typical for routine user laboratories is a combination of the uncertainty in the calibration doses, as stated by a primary or secondary standard dosimetry laboratory that performed the calibration irradiation, and the uncertainty in the ESR readout, which both contribute to the uncertainty in the calibration curve parameters (Bergstrand et al. 1998). If great care is taken, the achievable precision can be as low as 0.5 % for doses in the range of 5–25 Gy for dosimeters irradiated with ^{60}Co, including the uncertainties associated with primary dosimetry (Anton 2006). The main factors that might influence the amplitude of a radiation-induced ESR signal are the background signal and the temporal evolution of the radiation-induced signal due to changes in environmental conditions (temperature and humidity) (Alexandre et al. 1992).

Applications

Studies of clinical applications using ESR/alanine dosimetry started around the 1990s. An intercomparison among 16 Italian radiotherapy centers was done using the Istituto Superiore di Sanità (ISS) alanine dosimeters resulting in good agreement within tolerance levels of 5 and 6 % for reference and treatment condition, respectively, for a dose of 10 Gy of a high-energy photon beam (De Angelis et al. 2005).

Nowadays, new radiotherapy modalities [for example, intensity-modulated radiation therapy (IMRT), volumetric arc therapy or radiotherapy with heavy charged particles] are introduced in the clinics and challenge the requirement for dosimetry with respect to accelerator commissioning, dose verification and other quality control procedures. As a supplement to ionometry and calorimetry (that are difficult to apply in small fields), standard laboratories such as the National Physics Laboratory (NPL) in the UK and the Physikalisch-Technische Bundesanstalt (PTB), in Germany are adopting reference dosimetry based on ESR of alanine (Anton et al. 2008; Anton 2008; Helt-Hansen et al. 2009).

As an example, Kudynski et al. (1993) reported the first clinical trial of the application of ESR/alanine dosimetry to determine the radiation dose received by a patient in teletherapy cancer treatment with doses in the range of 0.6–8 Gy. They found that the absorbed dose in alanine could be determined with an accuracy of 3 % at low dose levels (0.6 Gy), whereas the error using thermoluminescence dosimetry (TLD) was 5 %.

In particular, some studies in vivo and in vitro using phantoms focused on doses and dose rates typical in brachytherapy. Schaeken and Scalliet (1996) reported their 1-year experience of the use of alanine dosimetry in radiotherapy. Commercially available alanine dosimeters from different manufacturers were tested in the dose range of 0.2–200 Gy of ^{60}Co gamma radiation. The repeatability was tested by measuring the standard deviation of the mean of ten readings resulting in a variation of 5 % (1σ) at dose levels $<$5 Gy and of 1 % (1σ) for doses $>$10 Gy. The usefulness of the alanine dosimetry system for clinical routine was illustrated by in vivo measurements during ^{92}Ir brachytherapy of cervix carcinoma, and the overall estimated uncertainty of the dose measurements was 5 % (1σ). Around the same time, Kuntz et al. (1996) reported applications of alanine–ESR in vivo dosimetry in radiotherapy. They found good agreement between calculated absorbed dose and the dose measured with alanine at high dose rate (HDR) present in brachytherapy and intra-operative treatments. A depth–dose curve with a 25-MeV X-ray beam was also measured, and comparison with doses obtained by means of an ionization chamber (IC) resulted in a difference of 6 %. Further, De Angelis et al. (1999) determined the absorbed dose rate in water per reference air kerma rate in vitro along the transverse bisector axis of a ^{137}Cs brachytherapy source. These authors measured the dose rate at different distances from the source using alanine dosimeters and determined the radial dose function along the transverse axis with an uncertainty of 3.4 % (1σ). The uncertainty in dose rate values was as 2.8 % (1σ) for distances from the source up to 7 cm.

To improve the spatial resolution in dose estimations of HDR ^{192}Ir source, Olsson et al. (2002a) used a thin alanine film and alanine/agarose gel around the brachytherapy source. They compared the experimental results with Monte Carlo simulations and found an agreement within 5 % of tolerance.

Calcina et al. (2005) determined the increment of dose delivered during the movement of the Ir-192 HDR source in the trajectory to its static position during brachytherapy treatment. They also determined the radial dose function and the transit dose values, for the first time using a first harmonic alanine–EPR dosimeter, and the results were close to those reported in the literature using TLD systems (Calcina et al. 2005).

Wagner et al. (2008) evaluated the potential of alanine/ESR dosimetry for quality assurance in 3D conformal radiotherapy (20MV X-ray beam) for prostate cancer. The measured dose accumulated at the anterior and the posterior rectal wall agreed with the applied dose within a mean deviation of 1.5 % (overestimation of the dose) and 3.5 % (underestimation of the dose). It was concluded that the alanine system is useful for quality control of irradiations in vivo.

Anton et al. (2009) studied in a phantom the dosimetry in the urethra using alanine/ESR during ^{192}Ir HDR brachytherapy of prostate cancer. The response of the alanine dosimetry system to the absorbed dose in water from ^{192}Ir was determined with a reproducibility of 1.8 % relative to ^{60}Co gamma radiation. The differences between the measured and applied dose were well within the limits of uncertainty, so the method was considered to be suitable for measurements in vivo.

Schaeken et al. (2010) applied alanine/ESR dosimetry to verify the total body irradiation (TBI) protocol and the dose calculation for treatment planning. The dosimetric system allowed accurate dose measurements enabling to validate the TBI dose protocol.

Other applications include the use of alanine/ESR for medical reference dosimetry which is possible due features such as the water equivalence of the system over a wide energy spectrum, its low signal fading and the possibility to perform nondestructive measurements and to use small dosimeters (Helt-Hansen et al. 2009). Also calibration of tomotherapy equipment has been successfully made (Perichon et al. 2011).

Challenges

Improvements in sensitivity

Investigations have been conducted adding high-Z materials as dopants to alanine, aiming at improvements of its sensitivity. These studies permitted important conclusions regarding the insertion of dopant materials in alanine dosimeters.

For example, the addition of potassium iodide (KI) in the alanine dosimeter in a small proportion (5, 10, 15 %) increased production of free radicals when irradiated with X-rays of lower energies (<100 kV), increasing the sensitivity (Chen et al. 2008). Of course, the loss of tissue equivalence must be weighed when these modifications are introduced.

According to the literature, the production of free radicals in alanine is due to direct interactions between the alanine molecules and photons. The presence of dopants with a high atomic number such as iodide promotes the release of a large number of electrons when low-energy photons hit the sample. The electrons ejected by the photoelectric effect have sufficient kinetic energy to produce further free radicals during interaction with alanine molecules, in addition to the radicals directly produced by interaction with photons. The released electrons are then responsible for triggering a series of chemical reactions involved in the formation of free radicals. Unfortunately, this gain in sensitivity comes at the cost of a reduced equivalence of alanine to the human tissue (Chen et al. 2008, 2010).

Similarly, Marrale et al. (2011) found an improvement in the sensitivity of alanine dosimeters when they doped them with gadolinium and exposed them to 6-MV photons at clinical doses.

More recently, Guidelli et al. (2012a) showed that nanostructured materials can be used for optimization of alanine sensitivity. They developed silver/alanine nanocomposites for radiation detection in medical applications and studied the influence of particle size on the detection properties. The sensitivity of dosimeters was optimized when silver nanoparticles (30 nm) that were well dispersed in the alanine matrix were employed. A similar result was found when gold nanoparticles dispersed in alanine were used (Guidelli et al. 2012b): The dosimeter sensitivity was improved almost 3 times using a nanocomposite containing 3 % (w/w) of gold. Therefore, the featured properties, such as homogeneity, nanoparticle size stability and enhanced sensitivity, make these nanocomposites potential candidates for the construction of small-sized radiation sensors for application in several medical procedures.

Further studies were performed searching other materials that are more sensitive or have simpler spectra than alanine. Examples of such materials are as follows: 2-methyl-alanine, lactate and sulfates of lithium and magnesium, ammonium tartrate, sulphanilic acid and malonic formats, ammonium, lithium and magnesium, dithionate lithium, trisodium citrate dehydrate, sodium tartrate dehydrate and taurine (Ikeya et al. 2000; Lund et al. 2002, 2005; Mack et al. 2002; Maghraby and Tarek 2006; Olsson et al. 2002b; Vestad et al. 2003; Tuner and Korkmaz 2010; Tuner and Kayıkçı 2012; Maghraby et al. 2012). Other works used alanine itself as a dosimeter incorporated to other materials. Olsson et al. (1996) aggregated alanine into agarose gel in an effort to build a three-dimensional

dosimeter that can be useful to evaluate dose distribution around brachytherapy sources.

Dosimetry of small fields

Some clinical applications such as IMRT and radiosurgery are characterized by the use of beams of high-energy and small radiation fields (<4 × 4 cm^2), and the presence of a high-dose gradient. In this case, the spatial visualization of the number of spins and the evaluation of the dose distribution in the region of target volume can be done by the technique of electron paramagnetic resonance image (EPRI).

EPRI has been developed in the 1970s. A summary of earlier studies can be found in Eaton et al. 1988. EPRI follows the same field gradient method as employed in nuclear magnetic resonance (NMR) imaging, where a field gradient is applied, superimposed to a uniform static magnetic field. The large line width of the ESR signal and the difficulty in the pulse microwave technique were the major problems in the development of EPRI (Ikeya 1993). For instance, no gradient encoding is possible because of the short T_1 signal (Eaton and Eaton 2012). For biological applications, a low microwave frequency (L-Band, 1.5 GHz) was employed; since then, the microwave loss is small and the penetration depth is on the order of 1 cm at this frequency. Most of ESR imaging studies have been done at this frequency using a loop-gap resonator (Ikeya 1993). Regarding dosimetric images, Morita et al. 1989 produced EPR images of radicals present in an organic solid dosimeter (alanine, polypropylene and sucrose) to investigate the dose depth profile after irradiation. They used an anti-Helmholtz coil attached outside of a rectangular cavity to produce a magnetic gradient of about 4 T/m along the sample. Pseudo 2D images were obtained after data acquisition at viewing angles from −90° to 90° at each 5° interval projections. The dose depth profiles agreed with theoretical considerations. Similarly, Yamamoto and Ikeya (1994) developed a system inserted into a TE_{011} cavity to produce high-linear magnetic field gradients of 1 and 2 T/m. They produced images of fossil carbonate, a burn wood and commercial alanine dosimeters irradiated with 30 kGy, in an X-band spectrometer. A set of measurements was performed after projections with steps of 5°. The 2D images of the spin distribution were produced after reconstruction using the back projection method.

More recently, Anton and Selbach (2006) reported a set of experiments with images of an alanine dosimeter produced in a Bruker ELEXSYS X-Band EPR imaging system. The system had three-axis planar gradients enabling production of 1D, 2D and 3D images, reconstructed from projections measured with a magnetic gradient of 0.48 T/m and a field sweep of 22.79 mT. Although it is possible to determine the depth–dose curve with a resolution of 0.1 mm with high signal-to-noise ratio, the deviation between experimental and calculated dose was up to 10 %. Then, the uncertainties associated with ESR images of radicals in alanine dosimeter were too large for clinical applications such as in radiotherapy, where the precision should be equal or <5 % at a confidence level of 95 %. Among the reasons cited by the authors were the large linewidth (0.5 mT for the central line) and low concentration of spins that could impose limits on the quality of the reconstruction.

In this sense, another alternative for dosimetry in IMRT and radiosurgery is the use of dosimeters of millimeter size, so-called minidosimeters, because a typical alanine/ESR dosimeter is 4.5 mm in diameter and 3–10 mm in height, i.e., too large to detect the field gradient.

Mack et al.(2002) were the first to report the use of minidosimeters (radius and height of 1 mm) in alanine dosimetry in radiosurgery. However, the minimum dose detectable in X-band spectrometer was as high as 150 Gy, making it impossible for practical use in clinical dosimetry in small radiation fields.

Chen et al. (2005) innovated the alanine/ESR dosimetry using a K-band (24 GHz) spectrometer, enabling the detection of lower doses in small dosimeters (Fig. 4). Minidosimeter composed b of DL-alanine with polyvinyl chloride (PVC) added in the proportion of alanine/PVC of 40/60 % was developed. The dimensions of dosimeters were 1.5 mm in diameter and 2.5 in mm height, and the mass was about 5 mg. With this system, doses as low as 5 Gy could be detected. The system was used to determine the beam profile of a field in a 3 × 3 cm^2 10-MV X-ray

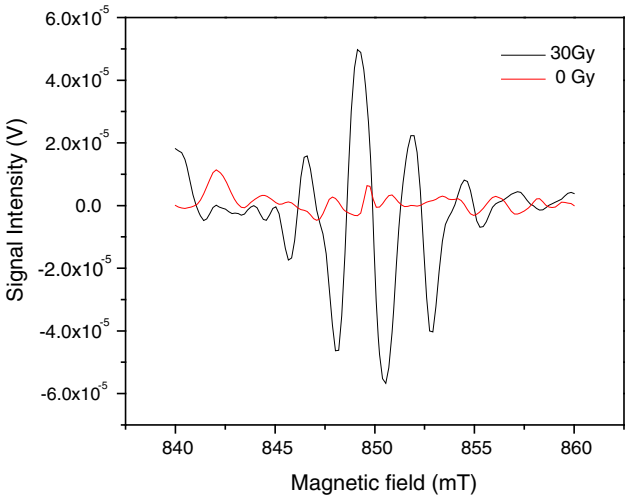

Fig. 4 K-band (24 GHz) spectra of an irradiated (^{60}Cobalt, 30 Gy) and non-irradiated minidosimeter of DL-alanine (dimensions 1.5 mm diameter, 2.5 mm height, 5 mg mass) showing the exceptional signal/noise ratio obtained at this frequency for such a small mass

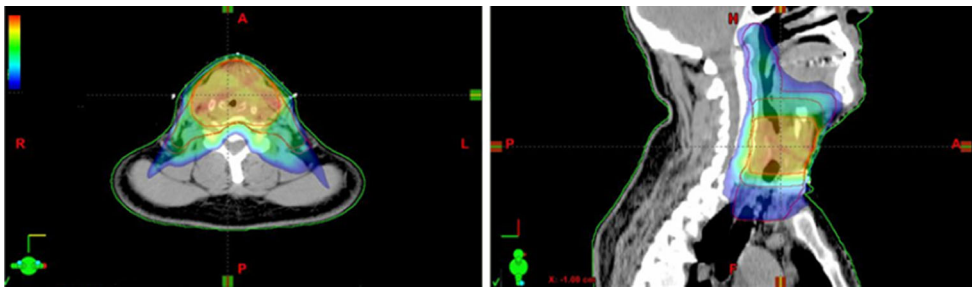

Fig. 5 Larynx treatment planning done concomitantly with 54, 59 and 70 Gy in three different PTVs, showing the *isodoses curves* decreasing in steps of 5 Gy from the inside to the outside (70 Gy, 65 Gy, 60 Gy and 55 Gy) delivered to the patient. *Left* picture axial view and *right* sagittal view, where *L* left, *R* right, *A* anterior, *P* posterior, *H* head and *F* foot

beam. Subsequently, to further reduce the lower limit of detection and improve the accuracy in determining the dose, Chen et al. (2007) changed the composition to L-alanine/paraffin and 2-methylalanine/paraffin with a ratio of 80/20 % and a nominal size of 1 mm in diameter and 3 mm in height, with a mass between 3 and 4 mg. With these two types of dosimeters, detection of doses as low as 0.5 Gy was possible using a K-band spectrometer. The dosimeters were applied to determine the relative output factors (ROF) and beam profile for small fields (e.g., 0.5×0.5 cm^2 and 1×1 cm^2) of a 6-MV X-ray beam that is used in radiosurgery. The dimensions of these minidosimeters allowed a spatial resolution comparable to that obtained with radiographic films when analyzed with a densitometer.

The sensitivity of pure alanine decreases by about 40 % for photons with energies <100 keV in comparison with ^{60}Co gamma radiation (Miyagawa and Gordy 1960), and an enhancement in sensitivity of alanine dosimeters to low-energy X-rays was achieved by doping the minidosimeters of L-alanine/polyvinyl alcohol (PVA) with potassium iodide (KI), enabling the application of ESR/alanine dosimetry in diagnostic radiology, which involves the use of photon beams of low energy (between 20–60 keV) (Chen et al. 2008). More specifically, the minidosimeters used were doped with potassium iodide (KI) in different proportions and irradiated with photon beams of different energies (80, 120, 250 kVp, ^{60}Co and 10 MV). The study reported an increase in sensitivity of almost five times to 120 kVp photons ($E_{eff} \sim 43$ keV) compared with ^{60}Co photons, for minidosimeters doped with 15 % KI, compared to undoped minidosimeters (only alanine) for which the sensitivity to 120 kVp photons was 4.5 times higher when compared to ^{60}Co. An even greater increase in sensitivity was found using lead iodide (PbI_2) as dopant (Chen et al. 2010). With these new doped minidosimeters, signals produced by doses as low as 10 mGy were detected, offering the possibility to apply them in diagnostic radiology and in other areas such as brachytherapy with sources of low energy such as ^{131}Cs ($\sim$30 keV), ^{125}I ($\sim$35 keV) and ^{103}Pd sources ($\sim$21 keV).

Other work using L-alanine/PVA (95/5 %) minidosimeters and K-band was performed to determine curves of percentage depth dose (PDP) in non-homogeneous (6-MV X-rays) and small fields ($0.5 \times 0\ 5$ cm^2) aiming to detect discontinuities in the PDP curve in air–tissue and bone–tissue interfaces. The experimental results were very similar compared to those obtained with radiographic films and Monte Carlo simulations using the PENELOPE code (Vega Ramirez et al. 2011).

The use of ESR/alanine minidosimeters in IMRT procedures provides a means of quality control in critical situations in which the complexity and criticality of the dosimetric profile requires the use of accurate methods. Figure 5 shows the simulation of treatment of a larynx using IMRT fields that was done in three different planning target volumes (PTVs). The treatment area is very near to the sensitive organs that must be spared. Therefore, this plan was very difficult to realize and involved high-dose gradients at various points. In this case, in the treatment planning and verification of the dose that would be delivered to the patient in a phantom, an IC could measure the dose at a point, while the alanine minidosimeters could measure the dose in PTVs and other nearby points in the high-dose gradients. This would provide very useful information, and it would additionally offer the practical advantage of measuring the dose at various points with a single exposure without having to change the position of the IC. This is just one of the many possibilities of new clinical applications of ESR/alanine dosimetry.

Conclusion

Alanine/ESR dosimetry fulfills many of the properties required for clinical applications such as a water-equivalent composition, a dose response independent of the energy

range used in therapy and a high precision. Nowadays, improvements in sensitivity and the development of minidosimeters coupled with the use of spectrometers of higher microwave frequency expanded the possibilities for clinical applications to the new modalities of radiotherapy (IMRT and radiosurgery) and to the detection of low doses such as those typical for some imaging techniques used in radiology. Certainly, these enhancements will contribute significantly to important clinical applications of ESR/alanine dosimetry.

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