On the Development of the VIPAR Polymer Gel Dosimeter for Three-Dimensional Dose Measurements

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Summary: The new polymer gel dosimeter, based on the modification of the VIPAR gel composition, is described for the purpose of radiation dose distribution measurement in radiotherapy. It features increased concentration of the two VIPAR substrates: *N*-vinylpyrrolidone (8%) and gelatine (7.5%) (*N,N′*-methylenebisacrylamide was maintained at 4%), and the addition of copper sulphate (0.0008%) and ascorbic acid (0.007%) in order to facilitate the preparation through elimination of the need for deoxygenation of the gel. Following the exposure to ionizing radiation, polymerisation and cross-linking of the new gel monomers occurs retaining the spatial distribution of absorbed dose and causing opacity of the gel. Quantitative parameters of the new gel dose response were studied using magnetic resonance imaging to relate polymerisation induced physicochemical changes of the gel to dose. The dose threshold is found significantly lower than that of the original VIPAR gel. The linear part of measured spin-spin relaxation rate $R_2(D)$ ($=1/T_2(D)$) reaches up to 35 Gy. Its slope and an intercept are slightly higher relative to the original VIPAR. The efficiency of the new polymer gel-magnetic resonance imaging dosimeter was also tested for dose verification of a 3D dose distribution planned by a commercially available treatment planning software (Eclipse External Beam v.6.5) and delivered by a 6 MV medical linear accelerator. The new polymer gel is proposed to be called, VIPARnd (after VIPAR-normoxic-double).

Keywords: gel dosimetry; ionizing radiation; radiotherapy; VIPARnd; VIPAR-normoxic-double

Introduction

High resolution, three-dimensional (3D) dose distribution measurement in radiotherapy has been facilitated for a few years now by means of polymer gel dosimetry. The method employs polymer gel dosimeter made of physical gel matrix including appropriate monomers. Under ionizing radiation monomers convert to crosslinked structures thus ''recording'' the absorbed dose distribution as a distribution of altered gel dosimeter physicochemical properties. The properties include the spin-spin relaxation rate ($R_2 = 1/T_2$) of the gel that can be measured by means of Magnetic Resonance Imaging (MRI) using optimised multi echo sequences. Acquired T_2 maps can therefore be converted to measured dose distributions after calibration.

We have proposed and effectively applied to radiotherapy dosimetry two soft tissue mimicking (water equivalent) gel dosimeters compositions known as PABIG and VIPAR.[1–3] The acronyms of these gel dosimeters were derived from the names

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of their ingredients. Both compositions consist of *N,N′*-methylenebisacrylamide, gelatine and water. Additional component of PABIG is poly(ethylene glycol) diacrylate, whereas VIPAR, *N*-vinylpyrrolidone. Both gel compositions can be used for dose measurements after purging them of oxygen using argon. Inter alia, these compositions feature an extended range of dose response facilitating the measurement of high spatial dose gradients involved in specific radiotherapy applications. Work is presently focused in ameliorating these compositions, i.e. reduction of their sensitivity to oxygen and UV light, optimization of the matrix of the polymer gels and improvement of their dosimetric characteristic (dose sensitivity and/or dose threshold). Some initial results on the modification of the VIPAR gel dosimeter are presented in this work.

Experimental Part

New Dosimeter Formula

The polymer gel dosimeter formula proposed in this work is based on that of the VIPAR polymer gel. In the new polymer gel the concentration of *N*-vinylpyrrolidone (NVP, Fluka) was doubled (8% w/v), as it was shown that it minimizes the dose threshold of VIPAR gel.[4] The concentration of *N,N′*-methylenebisacrylamide (MBA, Aldrich) was kept equal to 4% (w/v) as in the original VIPAR gel. Due to the higher concentration of NVP, the concentration of gelatine (Aldrich) was increased to 7.5% (w/v) to ensure appropriate stiffness and mechanical stability of the gel. Additionally, copper sulphate ($CuSO_4 \times 5H_2O$) and L-ascorbic acid (ASC), both Chempur, Poland, were added. These ingredients were used according to the suggestion of Fong *et al.*[5] for production of a polymer gel composition without the necessity of removing oxygen from its volume and therefore to simplify the manufacturing process. Several concentrations of these compounds were used to produce the gel formula ensuring the lowest dose threshold. In consequence, the optimal concentrations of $CuSO_4 \times 5H_2O$ and ASC were found to equal to 0.0008% (w/v) and 0.007% (w/v), respectively. The acronym VIPARnd (VIPAR-normoxic-double) is proposed for the new polymer gel composition.

Gel Preparation

VIPARnd was prepared by dissolving MBA in deionised water under stirring and heating below 50 °C. Afterwards, gelatine was added and completely dissolved before the solution was cooled down to a temperature of about 33 °C in order to add NVP. NVP was purified by distillation under reduced pressure (~80 °C, ~8 mbar) prior to its use. Finally, ASC and $CuSO_4 \times 5H_2O$ were added and the composition was thoroughly mixed. Vials chosen for irradiation and MR Imaging were filled completely with VIPARnd and they were closed either with rubber caps or Parafilm® foil.

No quantitative estimation of pre-irradiation storage effects on VIPARnd dose response were undertaken in this work. It was observed, however, that direct and prolonged exposure of VIPARnd to daylight should be precluded since it could initiate polymerisation of its monomers. A refrigerator (~10 °C) or a dark place at room temperature should be used. It was found that VIPARnd should be used maximum 4 weeks post-preparation, when it is kept in these favourable conditions. Results of this work correspond to VIPARnd gels irradiated 24 hours after preparation.

Irradiation

Two types of VIPARnd vials were used. Small vials (0.63 mm wall thickness, 8.75 mm inner diameter and 100 mm long), were exposed to cobalt ^{60}Co source (dose rate 0.02 Gy s^{-1}, Fricke dosimetry). Taking into account the relatively small diameter of these vials, the thin glass walls and the relatively high energy of the Cobalt source, a homogeneous dose delivery was achieved in the range of 0–120 Gy. To ensure this distribution, the glass vials were kept

rotating during irradiation. Larger vials (1 mm wall thickness, 25 mm inner diameter and 160 mm long) were used to record a dose distribution delivered by a medical linear accelerator (Clinac 2300 CD, Varian Medical Systems, Palo Alto, CA, 6 MV, 600 MU min^{-1}). Cubic phantom was prepared for dosimetry planning purpose (Figure 1) by tightly packing RW3 plates (polystyrene with 2% titanium dioxide TiO_2, density 1.045 g cm^{-3}) to form $18 \times 18 \times 18$ cm^3 cube. A hole for single large VIPARnd vial was centrally drilled and paraffin was used to ensure a proper fit (Figure 2). The phantom with VIPARnd vial was scanned using computed tomography (CT, Siemens Somatom + 4 expert, 1 mm step) and 3D image series were imported to the treatment planning system (TPS, Eclipse External Beam Planning 6.5, Varian Medical Systems, Palo Alto, CA) (Figure 1). Each sample was planned to receive three bands of different maximal dose with 5 cm spacing between the centres of consecutive bands. The total dose range was between 0 - 300 Gy. A four-field box technique was applied to irradiate each band (one field 3 cm × 3 cm at 0°, 90°, 180° and 270° gantry rotation). The Pencil Beam algorithm with calculation grid 2.5 mm × 2.5 mm × 1 mm was employed. Typical calculated dose distribution along the longer axis of VIPARnd vial is shown in Figure 1.

Relaxation Measurements

The NMR minispectrometer (Minispec 0.47 T, Bruker) was used to characterise the small, uniformly irradiated VIPARnd vials. The Carr-Purcell-Meiboom-Gill (CPMG) sequence with every second echo sampled, using 65 data points was employed to determine the spin-spin relaxation times (T_2). The time delay between consecutive 180° pulses was 40 ms and the first time-to-echo (TE) was equal to 40 ms. T_2 values were calculated on the basis of the first order exponential of free induction decay (FID). Measurements were performed at 25 °C (the heating–cooling system Haake, Germany; heating-cooling liquid – Fluorinert™ FC-43, 3M Company). The so-obtained T_2 values for each VIPARnd

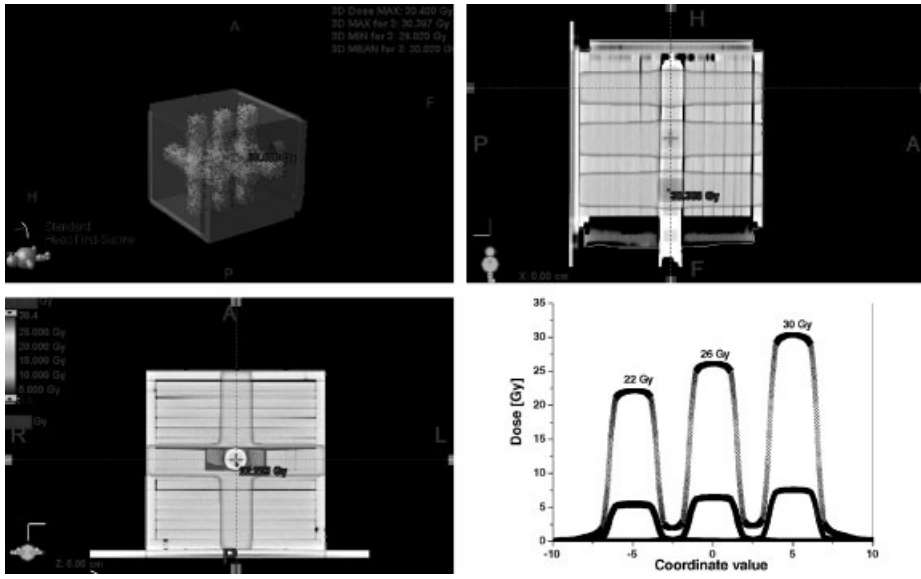

Figure 1.
Planning of the irradiation of the VIPARnd with the aid of Eclipse External Beam Planning 6.5. Upper-left – 3D output of TPS calculation of the LINAC dose distribution with a gel vial fixed inside the cubic phantom. The dose distribution inside the phantom with a gel vial: sagittal cross-section (Upper-right), transversal cross-section (Lower- left). Lower-right – an example dose distribution (three bands) along the longer axis of a gel vial.

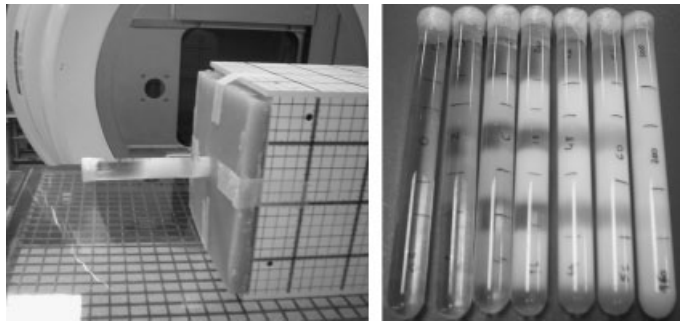

Figure 2.
Left – a view of VIPARnd gel vial partially removed from the cubic phantom and irradiated with the aid of medical accelerator visible in the background of the photograph. Right – large vials of irradiated VIPARnd (0–300 Gy).

sample were then converted to $R_2 = 1/T_2$ in order to gain a calibration curve of $R_2 =$ f(Dose).

The irradiated large VIPARnd vials (Figure 2) underwent an MR imaging (Picker Edge 1.5 T) applying a previously published protocol,[6,7] where TE = 30, 60, 90, 120 ms, TR = 2000 ms, 4 averages, 256×256 matrix, 1.09 mm pixel spacing. Four echo-based images for each irradiated vial were obtained (Figure 3). The pixel intensities of the four echo-based images in the central region of maximal absorbed dose of each band were taken to calculate T_2 relaxation times by fitting an exponential decay function in each set of four echo signal values. Then, the conversion of T_2 to $R_2 = 1/T_2$ was preformed to derive the calibration of $R_2 =$ f(Dose).

Results and Discussion

Exposure of VIPARnd to Ionizing Radiation

When VIPARnd is irradiated, the radical polymerisation and crosslinking of its monomers take place. Typically, for deoxygenated dilute aqueous solutions of vinyl monomers those reactions are initiated by the water radiolysis products: $^{\bullet}OH$, $^{\bullet}H$, or e^-_{aq}.[8,9] In case of the complex composition of VIPARnd that consists of 12% vinyl monomers, 7.5% gelatine and over 80% water, the polymerisation reactions are also likely to be initiated via water radiolysis

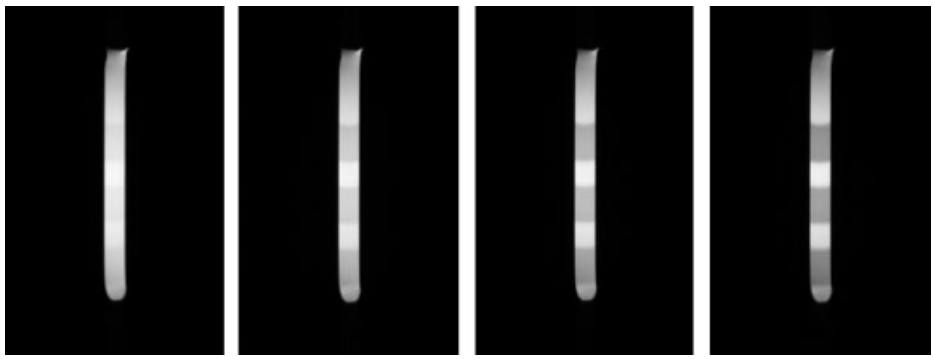

Figure 3.
Four echo-based MR 1.5 T images of a VIPARnd sample (from left: TE = 30, 60, 90, 120 ms). The regions of polymerisation and crosslinking of VIPARnd monomers, that are three dark grey bands of the maximal dose of 34, 36 and 40 Gy, can be discerned in the vial volume.

products, although the generation of free radicals via direct interaction of radiation with other substrates is probable. In order to eliminate the inhibition of polymerisation by oxygen, ascorbic acid and copper sulphate were used to bound free oxygen in VIPARnd volume. It is supposed that complexes of copper sulphate, ascorbic acid and oxygen are capable of initiating polymerisation of the monomers, as well.[5] For comparison, deoxygenation through saturation of the classical VIPAR composition with argon is done prior to irradiation,[2] as a prerequisite for polymerisation to occur, that otherwise would result in peroxides formation and inhibition of polymerisation reactions. Conversion of the monomers in VIPARnd occurs rapidly and large macromolecules are formed in the gelatine matrix. This product scatters visible light and therefore it can be discerned in the gel volume (Figure 2). It is distinctive feature of VIPARnd, that the absorption of only 1 Gy causes visible opacity in the irradiated band. The intensity of scattered light increases for bands of higher absorbed doses (Figure 2). Large polymeric aggregates in VIPARnd change the nuclear magnetic resonance (NMR) relaxation properties of the water protons in their vicinity. Therefore, the measured T_2 relaxation time values are different in various parts of the inhomogenously irradiated gel composition. This feature allowed us to derive a basic relation between the relaxation rate ($R_2 = 1/T_2$) and the absorbed dose for VIPARnd composition.

Basic Dosimetric Features of VIPARnd

The relaxation rates (R_2) of the irradiated bands of VIPARnd vials were related with the absorbed doses and the outcome is presented in Figure 4. The dose threshold, the intercept value, the full dose range, the linear dose range, and the slope of the linear dose range, were assessed form the dose response R_2 curves.

The results do not allow us to draw firm conclusions as to the exact threshold dose value. To do it, the response of the composition to the dose range 0–2 Gy should be meticulously re-examined. Nevertheless, it is clear the threshold dose is within 0.5–1.5 Gy. Full dose range of the composition is between 0.5–1.5 and about 120 Gy. However, no complete saturation was observed for doses over 120 Gy. The linear part up to 36 Gy was extracted form R_2-dose relations (Figure 4B) and the least squares method was applied to derive the intercept ($R_2(0)$) and the slope values. They equal to 1.331 s^{-1} and 0.0544 Gy^{-1} s^{-1} for 0.47 T NMR and 3.447 s^{-1} and 0.0888 Gy^{-1} s^{-1} for 1.5T MRI. The slope-to-intercept ratio at 0.47 T is 0.041 and 0.026 at 1.5 T, at 12% total monomer concentration. Original VIPAR composition (8% total monomer concentration) has a slope-to-intercept ratio 0.058 at 0.47 T (intercept 1.124 s^{-1}, slope 0.0651 Gy^{-1} s^{-1}) and

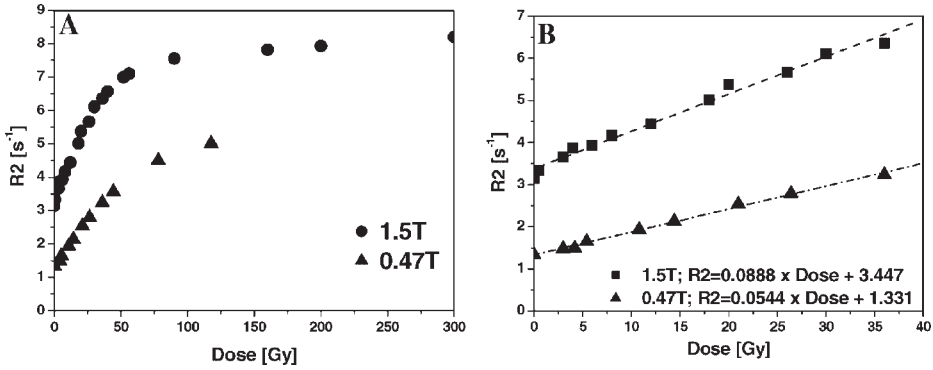

Figure 4.
A – Dose response R_2 curves for VIPARnd (NMR 0.47 and MRI 1.5 T) and the linear part of these curves (**B**).

0.052 at 1.5 T (intercept 1.528 s^{-1}, slope 0.0792 $Gy^{-1}\,s^{-1}$). For comparison, MAGIC gel composition has a slope-to-intercept ratio 0.077 at 0.47 T and 0.167 at 2 T at 9% monomer concentration.[5] The slope-to-intercept ratio is a way of determining dose resolution.[5] Therefore, to ensure appropriate dose resolution, it is not enough to increase the slope (by, e.g. increase in concentration of monomers that would lead to higher rate of propagation reactions as a result of higher probability of a monomer molecule to encounter another radicalised one[10]), but maximization of the slope-to-intercept relation, so minimization of the intercept value is necessary. The comparison of $R_2(D)$ for VIPARnd and VIPAR suggests that the lower slope-to-intercept ratio for the new composition is mainly due to increase of the intercept value. There can be a few reasons for the increase of the intercept: (1) higher concentration of gelatine in VIPARnd; unpublished data showed that the intercept of the original VIPAR was 0.735, 0.907, 1.273 [s^{-1}] for 3%, 5%, 7% gelatine (0.47 T, MBA and NVP constant, both 4%, Ar-saturated, measured directly post-irradiation); (2) marginal auto-polymerisation after gel preparation; (3) influence of other substrates: ASC and $CuSO_4 \times 5H_2O$. In Figure 5, the comparison of the $R_2 = f(Dose)$ of VIPARnd (8% NVP, 4% MBA, 7.5% gelatine, 0.007% ASC, 0.0008% $CuSO_4 \times 5H_2O$), double VIPAR (8% NVP, 4% MBA, 5% gelatine, argon) and original VIPAR (4% NVP, 4% MBA, 5% gelatine, argon) is shown.

It seems an increase in monomer concentration has less effect on the intercept than the presence of ASC and $CuSO_4$ in gel composition as well as higher gelatine concentration. Unpublished data showed that the intercept was equal to 0.907, 0.907, 0.954 [s^{-1}] for 8%, 4%, 2% NVP in original VIPAR (0.47 T, measured directly post irradiation).

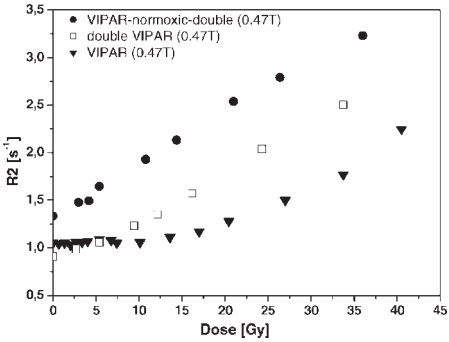

Figure 5.
Dose response (R_2) for VIPARnd, original VIPAR and double VIPAR [4] compositions (NMR 0.47 T).

In general, the alteration of VIPAR gel composition improved the dose-R_2 response in the lower dose region, because of minor dose threshold in comparison to the original gel. It is clear however, that the above-discussed parameters need further in-depth examination. In Table 1, a brief summary of the basic dosimetric parameters of VIPARnd and VIPAR is given.

3D Dose Distribution Verification

The unique feature of polymer gel dosimetry is the ability to measure absorbed dose distributions in three dimensions. For this reason, it is readily used for verifications of dose distributions calculated by treatment planning systems. VIPARnd calculated 3D data (using the obtained calibration curve) are compared to TPS calculated dose distribution. In Figure 6, the dose profiles for 18 Gy and 26 Gy bands are shown along with corresponding TPS data.

Table 1.
Comparison of basic dosimetric parameters of VIPARnd and the original VIPAR gel dosimeters (based on $R_2(D)$ measured ~20 h post-irradiation).

1.5 T MRI	Full dose range [Gy]	Linear dose range [Gy]	Intercept [s^{-1}]	Slope (sensitivity) [$Gy^{-1}\,s^{-1}$]	Slope-to-intercept ratio
VIPARnd	0.5–1.5–120	0.5–1.5–35	3.447	0.0888	0.026
VIPAR	8–700	8–35	1.528	0.0792	0.052

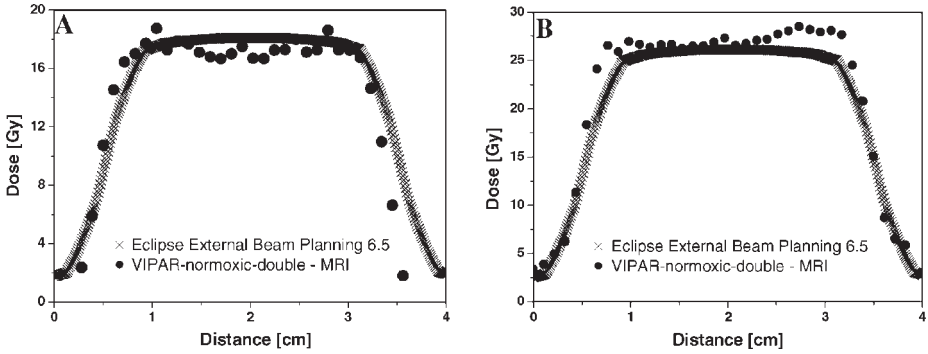

Figure 6.
The comparison of the VIPARnd-MRI measured and Eclipse External Beam Planning 6.5 calculated the dose distributions for two bands of predicted maximal dose of 18 Gy (**A**) and 26 Gy (**B**).

On the whole, the dose distribution measured by VIPARnd-MRI method overlaps the calculated one. The characteristic feature of VIPARnd is that it enables measurements of doses much lower than the original composition, at least 2 Gy, as can be seen in Figure 6. However, in some points of the graphs the lack of overlapping can be seen. This might be caused by the MR image quality,[11] since thorough analysis of the MRI data revealed that in some areas the data was misshapen by artefacts. The gel data in plateau region present possible inability of VIPARnd to well record flat dose regions due to relatively low dose resolution and probably high signal-to-noise ratio (SNR) in MR scanning. This can be overcome when taking into account the whole 3D data and fitting profile lines.

Conclusions

VIPARnd shows potential for radiotherapy dosimetry. The procedure of its preparation has much been facilitated thanks to elimination of deoxygenation step and application of O_2 bonding substrates. Doubling *N*-vinylpyrrolidone concentration significantly reduced the threshold dose typical for the original VIPAR gel. Further examination of the MR scanning procedure on the base of adopted protocol[6,7] is ongoing for to eliminate effects influencing dose distribution measurements as well as re-examination of $R_2(D)$ relation for VIPARnd is considered to precise and verify basic parameters of the gel.

In view of the promising results on VIPAR modification, a similar approach has been applied to examine the possibility of normoxic PABIG preparation. The results are likely to be publicised in due time.

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