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Abstract	Radiotherapy widely uses the polymer gel dosimeter. The advantage of polymer gel dosimetry is the mapped 3D absorbed dose distribution that other dosimeters cannot achieve. The Acrylamide (AAm) is a frequently used monomer; however, the extreme toxicity of Acrylamide (ORL-RAT LD50: 124 mg/kg) raises a concern. Therefore, this study developed a new type of Propylene acid based gel dosimeter, named DEMBIG gel. The following outlines the aim of this study: (1) using two-point formulation to find the optimal scan parameter of MRI according to the best sensitivity and linearity (correlation coefficient) of DEMBIG gel, (2) using the optimal scan parameter of MRI to observe the properties of DEMBIG gel, and (3) verifying the three-dimensional (3D) dose distributions of radiotherapy. This study obtained three major results: 1. The scan protocol of MRI was established. 2. The preliminary results of DEMBIG gel were: (1) The range of absorbed dose of DEMBIG gel: 0–20 Gy. (2) The sensitivity and correlation coefficient of DEMBIG gel at verification as slope: 0.181 sGy^{-1}, R^2:0.997. (3) There is no energy dependency of the DEMBIG gel. (4) The dose difference was 3% in the three-dimensional (3D) isocenter dose in clinical radiotherapy. These data show that DEMBIG gel is a potential candidate for the 3D dosimeter.

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Preliminary investigation of a new type of propylene based gel dosimeter (DEMBIG)

Bor-Tsung Hsieh · Chi-Tsung Chiang · Pi-Hui Hung · Chia-Hung Kao · Ji-An Liang

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Abstract Radiotherapy widely uses the polymer gel dosimeter. The advantage of polymer gel dosimetry is the mapped 3D absorbed dose distribution that other dosimeters cannot achieve. The Acrylamide (AAm) is a frequently used monomer; however, the extreme toxicity of Acrylamide (ORL-RAT LD50: 124 mg/kg) raises a concern. Therefore, this study developed a new type of Propylene acid based gel dosimeter, named DEMBIG gel. The following outlines the aim of this study: (1) using two-point formulation to find the optimal scan parameter of MRI according to the best sensitivity and linearity (correlation coefficient) of DEMBIG gel, (2) using the optimal scan parameter of MRI to observe the properties of DEMBIG gel, and (3) verifying the three-dimensional (3D) dose distributions of radiotherapy. This study obtained three major results: 1. The scan protocol of MRI was established. 2. The preliminary results of DEMBIG gel were: (1) The range of absorbed dose of DEMBIG gel: 0–20 Gy. (2) The sensitivity and correlation coefficient of DEMBIG gel at verification as slope: 0.181 sGy^{-1}, R^2:0.997. (3) There is no energy dependency of the DEMBIG gel. (4) The dose difference was 3% in the three-dimensional (3D) isocenter dose in clinical radiotherapy. These data show that DEMBIG gel is a potential candidate for the 3D dosimeter.

Keywords Polymer gel dosimeter · 3D dosimeter

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Introduction

Radiation therapy can induce many significant biological and chemical effects to tumor cells and surrounding normal tissue. Verifying radiation treatment planning is important to not only deliver an adequate prescribed dose to the target volume, but to also spare critical organs at risk, especially for application in radiosurgery.

Many systems of chemical dosimetry have been proposed with great achievement in the recent years, such as Fricke dosimeter [1], film, solid state methods, silicon diodes and other aqueous dosimeter [2, 3]. We may select the proper dosimeter based on their unique character.

Wagter [4] proposed the terms of an ideal dosimeter in 2004. Traditionally, the dosimeter used for verification in radiation oncology can only show a 2D dose map.

Polymer gel, a chemical dosimeter that reacts with the monomer and free radicals at the irradiated area, has the unique advantage to offer 3D dose distribution. The degree of polymerization is proportional to radiation dose. Alexander et al. [5] first proposed the polymer system to

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determine the effects of ionizing radiation on polymethylmethacrylate. Maryanski [6] first proposed the PAG gel with acrylic monomers and *N,N′*-methylenebisacrylamide, named BANANA in 1993.

Recently, we used the less toxic material (DEMA, 2-(Dimethylamino) ethyl acrylate, ORL-RAT LD50:1751 mg/kg [7]) as a monomer in composition with the new polymer gel named DEMBIG (2-(*D*imethylamino) *e*thyl acrylate, *N′N′-m*ethylene-*bi*sacrylamide, *G*elatin).

This research used MRI as a measurement method of DEMBIG gel to obtain an optimal scan parameter to verify the correlation coefficient of dose response, temporal stability of dose response, and energy dependence for DEMBIG gel by optimal MRI parameters. This study also used DEMBIG gel and optimal MRI parameters to simulate the radiotherapy process and to verify the isocenter dose.

Materials and methods

Polymer gel manufacture

The composition of DEMA gel were Gelatin (Sigma-Aldrich 7%), 2-(Dimethylamino) ethyl methacrylate (DEMA, Sigma-Aldrich 5%), *N′*,*N′*-methylene-bisacrylamide (BIS, Merck Chemical Company 4%), and deionized water prepared under a controlled argon atmosphere inside a glove box. To begin gel manufacture, the water was filled with argon (20 psi/min) for 20 min, followed by adding gelatin to the water and magnetically stirring for 10 min at room temperature. The solution was further heated and stirred to 45 °C to dissolve the gelatin. After 15 min, DEMA and BIS were added to the solution and kept magnetically stirred for 30 min until complete dissolution. Finally, the gel was filled with argon for 30 min and then poured into Pyrex screw test tubes (16 mm OD, 100 mm length, No. 9826,) and wrapped in aluminum foil to prevent photo-polymerization, and placed in a refrigerator (4 ± 1 °C) for 48 h to irradiate.

Irradiation of the gel

Irradiation was performed by a linear accelerator (Clinac 21 EX, Varian Medical Systems, Palo Alto, CA, USA). The center of the short side of a customized 30 cm × 30 cm × 4 cm acrylic phantom was punctured with a 16 mm diameter hole, to accommodate the Pyrex test tube. To discover the precise location, 3.5 cm and 16.5 cm acrylic sticks were placed in the upper and lower sides of a test tube. Acrylic phantom was placed in the middle between two pieces of 3 cm solid water phantoms. The setup criteria of the linear accelerator were: gantry: 0°, field size: 10 × 10 cm^2, depth: 5 cm, photon energy: 6MV.

Magnetic resonance imaging

The T2 relaxation times of gel samples were determined 24 h after irradiation, using a head coil in the MRI facility (Signa 0.5 T, GE Medical System). The vials were imaged upright in a single slice in the axial plane at 22 °C using a 2-echo spin-echo sequence. Dose–response curves were calculated by taking the mean (and standard deviation) of a region of interest within each vial. All calculations were performed using Image J (free software). This study used fast spin-echo sequences to acquire optimal echo time, the formula of *R*2 calculation as formula (1)

$$R2 = \frac{1}{T2} = \frac{1}{\mathrm{TB2} - \mathrm{TB2}} \times \frac{S(\mathrm{TB2})}{S(\mathrm{TB2})} \quad (1)$$

The two acquired images matched the long echo time and the short echo time. The DEMBIG gel was imaged by the spine echo sequence and the fast spine echo sequence in 14 protocols. The spine echo sequence set of TE matches using TE1 are as follows: 30, 40 ms and TE2: 100, 120, 130, 140, 150, 160, 170, 180 ms with TR of 3 s, slice thickness of 5 mm, FOV of 256 mm. The fast spine echo sequence set of TE matches were TE1:31.5 ms and TE2:158 ms, the other parameter was the same as the spine echo sequence. Table 1 lists the parameter setting of MRI.

Verification of dose distribution in radiotherapy

As a base for treatment planning, CT-images of the gel phantom were acquired using a spiral CT scanner (Hispeed NX/I, GE Medical System). The slice thickness was 2 mm. We used the treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) to generate the 6 MV radiosurgery plan, with gantry angle rotation 0, 72, 144, 216, 288 degree and the prescribed target dose of 20 Gy. The output was 400 MU/min during radiation. A 270 mL gel phantom was irradiated by a linear accelerator. There were six vials for the calibration curve.

Table 1 Scan parameter setting of MRI

Parameter	
Matrix size (MS)	256 × 256
Slice Thickness (mm)	5
Repetition Time (ms)	3000
Echo Time 1_short TE1 (ms)	31.5, 30, 40
Echo Time 2_long TE2 (ms)	100, 120, 130, 140, 150, 158, 160, 170, 180
Number of slices	9
Number of echo	2
Bandwidth (Hz/pixel)	10.42

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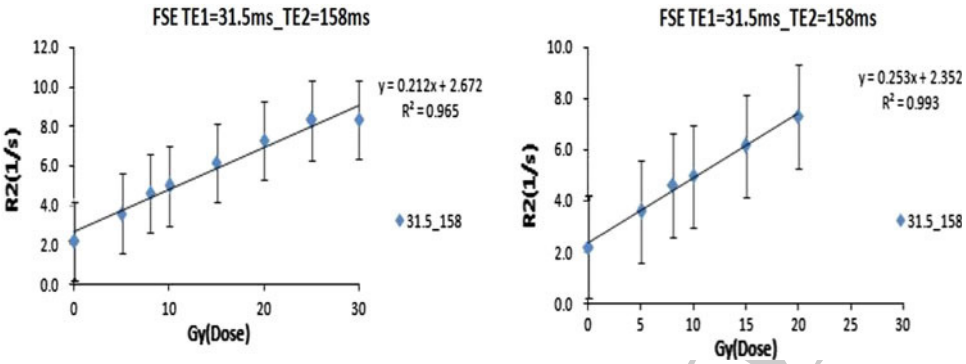

Fig. 1 Dose response curve of DEMBIG gel at optimal TE match protocol

Results

Optimal scan parameter-Echo Time, TE

DEMBIG acquired the image of optimal echo times by a fast spin-echo sequence, analyzing the relationship between *R*2 and the absorbed dose by a two-point method at different ranges of dose response. The *R*2-dose response of the DEMBIG polymer gel dosimeter was linear between 0 and 30 Gy doses. Figure 1 shows the dose response curve of DEMBIG gel at optimal TE match protocol. The fast spine-echo sequence set of the TE1:31.5 ms and TE2:158 acquired superior *R*2-dose sensitivities and correlation coefficient. We found an improved correlation coefficient at 0–20 Gy compared to 0–30 Gy, when the absorbed dose over 25 Gy the DEMBIG was saturated.

Verification optimal protocol of MRI

Correlation coefficient of dose response

The DEMBIG polymer gel formulation by % mass consisted of 4% *N*,*N*′-methylen-bis-acrylamide (bis), 5% DEMA, and 7% gelatin irradiated up to 20 Gy and imaged by MRI optimal protocol. Table 2 lists the optimal setting.

Figure 2 shows the DEMBIG gel for three batches using the optimal protocol.

Temporal stability of DEMBIG gel

The DEMBIG gel was irradiated up to 30 Gy and imaged at 2, 4, 6, 12, 18, 24, 48, and 72 h respectively. Figure 3 shows the correlation coefficient of 0–30, 0–25, and 0–20 Gy, including the temporal stability of DEMBIG gel at 24 h in 0–20 Gy after post irradiation.

Table 2 Optimal setting of MRI

TE1 (ms)	TE2 (ms)	TR (ms)	Thickness (mm)	Scan sequence
31.5	158	3000	5	Fast spin echo

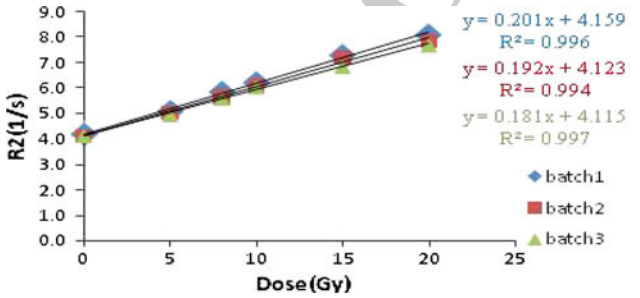

Fig. 2 Reproduction of DEMBIG gel for three batches using optimal protocol

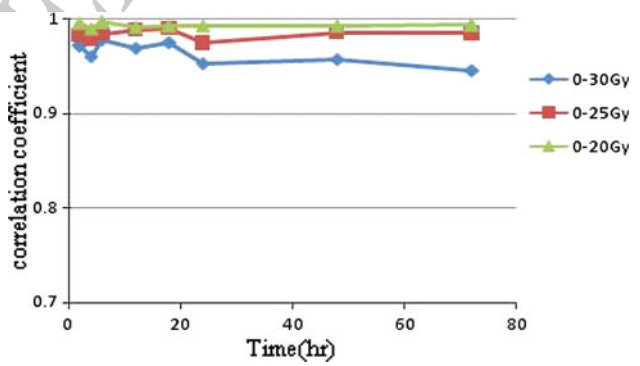

Fig. 3 Temporal stability of DEMBIG gel

Verification energy dependence of DEMBIG gel dosimeter

Figure 4 shows the DEMBIG gel dosimeter *R*2-dose response with different photon energies; therefore no significant energy effects in DEMBIG gel have been observed using the optimal protocol of MRI evaluation when photon energy used 6 and 10 MV.

Verification of isocenter dose in clinical practice

Figure 5 shows calibration *R*2 dependence on the absorbed dose for DEMBIG gel at optimal MR setup. The data revealed no significant difference in dose sensitivity and *R*2 (0) parameters, which were important for further

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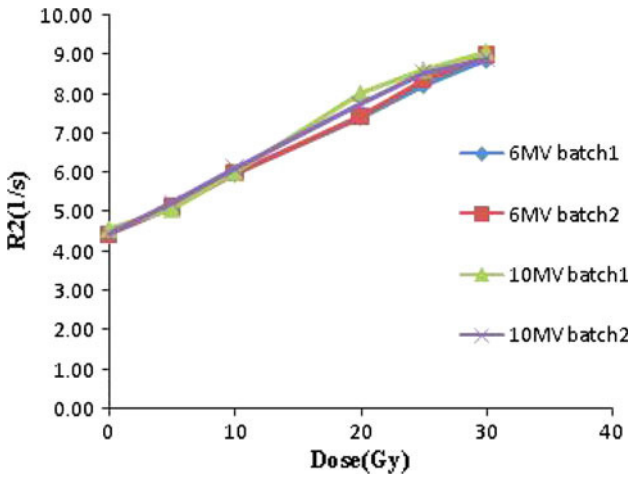

Fig. 4 Energy dependence of DEMBIG gel

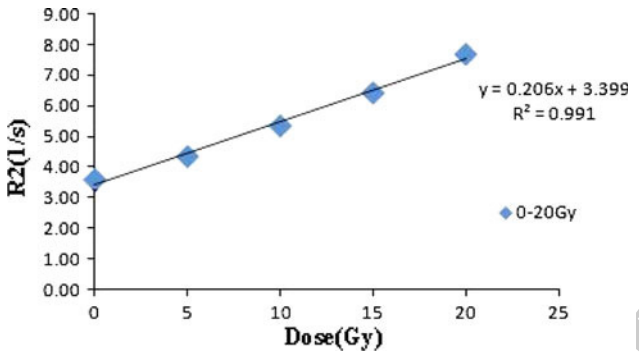

Fig. 5 Calibration *R*2 dependence for DEMBIG gel

Table 3 Comparison of isocenter dose with treatment plan and DEMBIG gel

Item	Does of isocenter (Gy)	Dose percent of isocenter (%)	Difference (%)
Treatment plan	20	100.1	0
DEMBIG gel	20.41	102.0	2

calculations of dose distribution. The fit curve function is $R2 = 3.399 + 0.206D$ with a dose range of 0–20 Gy. The isocenter dose of 270 ml gel phantom is 20.41 Gy using the fit curve function. Table 3 compares the original treatment plan with the gel phantom. The difference was 2% compared with the original treatment plan.

Discussion

Accurate measurement of absorbed dose from ionizing radiation is important. The DEMBIG gel is one hydrogel of chemical dosimeter with feature of water or tissue equivalent and operation dose range was from 0 to 20 Gy read out by MRI to fit in clinical application.

Table 4 Sensitivity of different polymer gel formulations [5]

No.	Type	Sensitivity (1/s)
1	PAG	0.33
2	PAGAS	0.008
3	nMAG	2.1
4	HEMA	0.046
5	DEMBIG	0.181

Free radical reactions initiate the gel polymerization process. Nevertheless, molecular oxygen is an efficient "scavenger" of free radicals and inhibits polymerization of the gel dosimeter. The polymer gel dosimeter includes hypoxic and anoxic gel dosimeters.

Tetrakis (hydroxymethyl) phosphonium chloride (THPC), a new antioxidant, can solve the oxygen problem. Formulation of DEMBIG gel did not put in the THPC as an antioxidant, because the pH value of DEMBIG is 14 and THPC is 3, solidifying the solution from neutralization. Another method to remove oxygen uses nitrogen or argon as an antioxidant. Argon (20 psi/min) replaces oxygen with a concentration below 1% in the fabrication process to prevent the oxygen from dissolving into the solution.

De Deene [8] mentioned MRI as a non-destructive measurement method of the gel dosimeter in his review article. The MRI takes the *R*1 mapping sequence; *R*2 mapping sequence, and magnetization transfer (MT) to obtain an image for mapping dose distribution. Polymer gel dosimeters are based on the conversion of comonomers to polymer aggregates upon irradiation. This reaction alters the mobility of surrounding water molecules, resulting in a change in *R*1 and *R*2. The dose–response of *R*2 in gelatin based polymer gel dosimeters, however, is more pronounced than that of *R*1. The *R*2 mapping sequence uses single- spin echo sequence, fast single-spin echo sequence, and multi-spin echo sequence for measuring the gel dosimeter.

The most important consideration of the polymer gel dosimeter is the correlation coefficient and dose response sensitivity. The range of dose response and sensitivity of DEMBIG gel were 0–20 Gy and 0.181(1/s), respectively. Jirasek listed the sensitivity to radiation of different polymer gel formulations [9], shown in Table 4. He investigated polymer gel solutions with various gelling agents, such as gelatin and agarose. The gel dosimeter used gelatin as gelling agents to improve sensitivity on MRI due to a low background. Overall sensitivity was between 0.008 and 2.1(1/s). The sensitivity of the DEMBIG dosimeter was 0.181(1/s) in gelatin with development potential. Future

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work needs to prove the other physical properties of clinical perspectives with DEMBIG.

In conclusion, the optimal scan parameter of MRI as a measurement method of DEMBIG gel were short TE:31.5 ms, long TE:158 ms, TR = 3 s, slice thickness = 5 mm, FOV 256*256 using the fast spin echo. The range of dose response was 0–20 Gy, correlation coefficient difference was 0.997, sensitivity was 0.181(1/s), and temporal stability at 24 h for DEMBIG gel was based on the MRI optimal scan parameter. DEMBIG gel does not possess energy dependence. The difference of DEMBIG gel was less than 3% at 0–15 Gy in verifying isocenter dose in the clinical radiosurgery process. These data show that DEMBIG gel is a potential candidate for the 3D dosimeter.

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