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Original Article

The thermal measurement by the normoxic methacrylic acid gel had been irradiated radiation

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Purpose: In studying normoxic polymer gel dosimeters development, researchers have shown the influence of the temperature history during storage of the gel dosimeter on the dose response curve for two gel dosimeters using the acrylamide based gel dosimeter (nPAG) and methacrylic acid (nMAG). It was found that the methacrylic acid based gel dosimeter is more heat-sensitive than the acrylamide based gel dosimeter upon cooling. The purpose of this study was to fabricate a normoxic methacrylic acid based gel dosimeter that could be used as a thermal dosimeter which is proportional to the temperature in the tissue surrounding lesions of typical thermal therapy.
Methods: Thermal dosimetry aims to quantify heat-induced tissue damage based on knowledge of the tissue's temperature profile. This quantitative framework is particularly useful for assessing the biological effects of hyperthermia cancer treatments in clinically-relevant terms. We approach a new way that using the gel dosimeter to evaluate the thermal response. The thermal response of these gels was often investigated by a technique based on magnetic resonance imaging. MRI was undertaken approximately 24 hour after the heating.
Results: The thermal response of the current methacrylic acid based gel was haracterized over 22 – 60°C using MRI measurements. The results showed that R^2 values were higher than 0.9885 and the performance were also consistent at radiation dose greater than 15Gy.
Conclusion: The experiment established that nMAG gel dosimeters have a good linear response for thermal change ranging from 22-60°C after radiation. We consider that 10-15Gy of radiation dose is a better choice to irritate because excessive dose causes the warming phenomenon on the gel.

Keywords: nMAG gel, MRI measurements, thermal dosimetry, thermal therapy

1. Introduction

Traditionally, surgery has been the only cure for many solid tumors. Technological advances have catalysed a shift from open surgery towards less invasive techniques. Laparoscopic surgery and minimally invasive techniques continue to evolve, but for decades high-intensity focused ultrasound has promised to deliver the ultimate objective — truly non-invasive tumor ablation. However, with recent improvements in imaging, has this objective finally emerged as a real clinical possibility (1). High-temperature thermal therapy is currently being implemented as a minimally-invasive alternative to traditional surgery in the treatment of benign disease and cancer, as well as repair of sports injuries and tissue re-shaping or modification.

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Many different types of energy sources are applied, including laser, radiofrequency (RF) current, microwave, ultrasound and thermal conduction based devices. Heating energy can be applied by external means or internally via interstitial, intraluminal or intracavitary approaches. The use of high-temperature thermal therapy is prevalent, with increasing commercial interest and clinical implementation. New heating technologies with improved precision or control of the heating patterns, combined with non-invasive MR thermal monitoring or other image-based approaches, have potential to improve accuracy and verification of therapy delivery which is most critical for the treatment of cancer (2,3). The technology is prevalent and in various levels of advancement, with the move toward more spatially-accurate and controllable heating systems combined with image-guidance and treatment verification warranted, especially for the treatment of cancer (3-6). A problem that is common to all hyperthermia treatments, whatever the energy source for heating, is the necessity to know the temperature distribution within tissue because there is a narrow therapeutic window between temperatures that are toxic to cells (> 42°C) and those that are not (< 41.8°C) (7). Therefore, thermal dosimeters and volumetric heat-sensitive gels have gathered great importance in clinical thermal therapy.

Polymer gel dosimetry has certain features that make the technique unique for radiation dosimetry including the potential for measuring three-dimensional absorbed radiation dose distributions (8-10). As the absorbed dose increases, the monomers polymerize to form a solid polymer within the gelatin matrix. The concentration of monomers remaining in the gel has been found to decrease mono-exponentially as a function of absorbed dose (11). In addition, a higher sensitivity for the irradiation temperature was found in a normoxic methacrylic acid based dosimeter gels (12-14). As the movement of water molecules, monomers and polymer structures in solution increases with temperature the dipole-dipole interactions will be less efficient. As a result, the R_2 of polymer gel dosimeters will decrease with increasing temperature (12-16).

The purpose of the study was to fabricate a normoxic methacrylic acid based gel dosimeter that could be used as a thermal dosimeter which is proportional to the temperature in the tissue surrounding lesions of typical thermal therapy. In previous research, we have initially implemented this function (15,16). We approach a new way that using the gel dosimeter to evaluate the thermal response. The thermal response of the current methacrylic acid based gel was characterized over 22 – 60°C using MRI measurements. More specifically, this study was undertaken in order to understand how the nMAG gel has higher temperature sensitivity.

Materials and Methods

Gel fabrication and irradiated radiation dose

The nMAG gel was fabricated under normal oxygen atmosphere according to Karlsson et al. (17). The composition of nMAG gel dosimeter was listed in **table 1**. Methacrylic-acid-based gels were prepared consisting of distilled water, gelatin (300 bloom, Sigma Chemical Co.), methacrylic acid (MA, Wako Pure Chemical Co.), and tetrakis-hydroxymethyl-phosphonium chloride (THPC, 80%, Sigma Che- mical Co.) as an oxygen scavenger. This type of gel composition is called MAGAT (Methacrylic Acid, Gelatin And THPC)(17,18). Each sample was prepared in a 200ml beaker under normal atmospheric conditions. After the water wash heated to 60°C, gelatin was added and dissolved using a magnetic stirrer.

The gelatin solution was cooled to 50°C, then methacrylicacid and THPC were added to the gel. The resulting solution was poured into test tubes (diameter 16 mm, wall thickness 1 mm, and length 100 mm) until overflowing to avoid oxygen contamination from air. The top of each tube was sealed with polyvinyl-chloride (PVC) film and tightly closed with a polypropylene screw cap. After fabrication,

Table 1. The composition of nMAG gel dosimeter.

Chemical component	Concentration
Gelatine	8%
Methacrylic acid(MAA)	2%
Tetrakis(hydroxymethyl) phosphonium chloride(THPC)	2mM

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all samples were stored in an incubator at a fixed temperature (4°C) for one day to avoid effects of temperature variations before irradiations (12,13).

The irradiations were performed using a 6MV photon beam of an Elekta Synergy Linear Accelerator (Elekta Synergy; Crawley, UK). The axis of test tube was perpendicular to the beam. The SSD was 100 cm, and the wide field size of 40x40 cm2 was used to guarantee the beam flatness. The deviation of dose is less than 1% in the center of approximately 10x10 cm^2 where test tubes were irradiated. A test tube was set between two Solid Water phantoms (GAMMEX) as shown in **Figure 1**. In the both irradiations, the beams were delivered 5, 10, 15, 20 and 50 Gy to the test tubes with the fixed dose rate at 100 cGy/min.

Refrigeration in 4°C during 24 hours, the gel dosimeter was heated in water bath until heated to the specific temperature, from 24℃ to 60℃ in 2℃ increments, and hold the temperature for 10 mins. Before scanning, the gels had been left in the air conditioned scanning room to equilibrate to an ambient temperature of 22°C. Figure 2 shows the schematic diagram of the operating process.

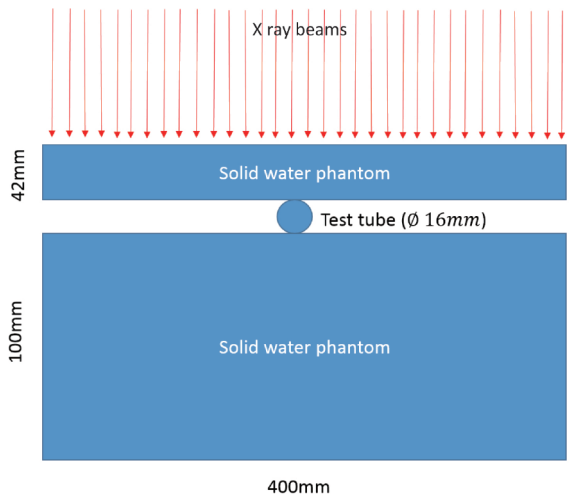


Figure 1. Schematic diagram of experimental set up for gel irradiated 19.

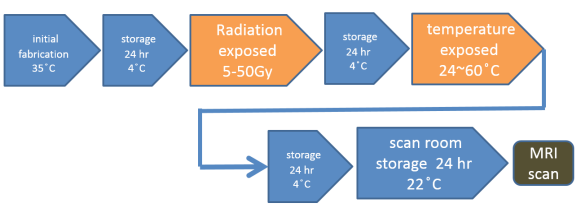


Figure 2. The schematic diagram of gel fabrication, storage, radiation exposure, temperature exposed and MRI scan.

MR scanning

Thermal response of these gels was often investigated by a technique based on magnetic resonance imaging. MRI was undertaken approximately 24 hour after the heating. MRI measurements were performed using a Siemens Sonata 1.5T scanner (Siemens Medical Solutions Erlangen, Germany) and the 8 channel head coil receiver. In this experiment, we manufactured a water phantom to house the polystyrene test tube. A customized multiple-spin-echo pulse sequence was developed to acquire 32 spin echoes with an optional choice of echo spacing(ESP) from a minimum of 22.5 ms. The parameters of the multi-echo imaging protocol were as follows: TR =4500 ms, slice thickness 20 mm, number of acquisitions = 2. The number of slices is 3.

After obtained the T2 relaxation images, we computed the value of R_2 under different temperatures with region of interest (Region of interest) analysis by using MATLAB® (the Mathworks) program.

Results

Analysis of data acquired for 5 groups of the experiment at various water bath temperatures from 22 to 60℃ yields two observations of interest. The first is that the percentage of denatured protein reaches a temperature-dependent steady-state value (**Figure 3**). Under the temperature range of 22 to 60℃, the R_2 values of 5Gy group were 12.5039 ± 0.01434 to 0.2598 ± 0.0861 (s^{-1}), the R_2 values of 10Gy group were 19.6027 ± 0.02634 to 1.0611 ± 0.1094 (s^{-1}), the R_2 values of 15Gy group were 23.4837 ± 0.0305 to 4.8269 ± 0.1182(s^{-1}), the R_2 values of 20Gy group were 24.412 ± 0.0289 to 4.8279 ± 0.0914 (s^{-1}), the R_2 values of 50Gy group were 25.0909 ± 0.0450 to 4.9508 ± 0.1693(s^{-1}), respectively. When the temperature increased, the R_2 value decreased linearly. The trend produced a high degree of linearity (R^2 = 0.9865- 0.9993) over this temperature regime (22-60°C).

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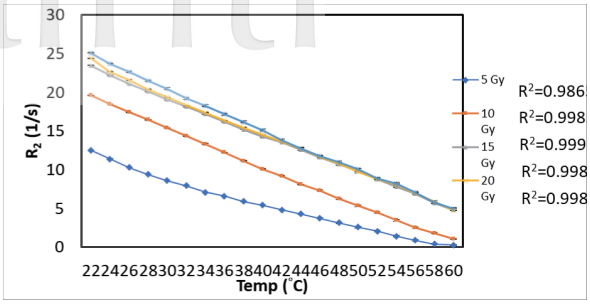


Figure 3. Temperatures - R_2 plots for a nMAG polymer gel dosimeter scanned at various radiation dose.

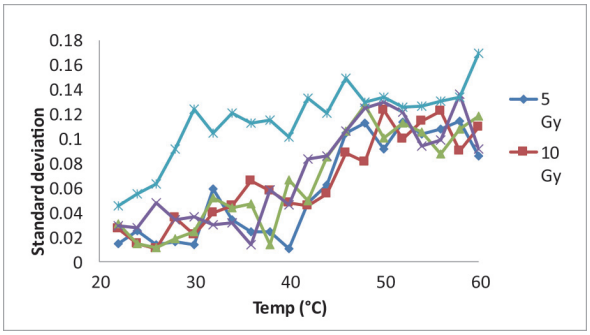


Figure 4. The standard deviation of R_2 plots for a nMAG polymer gel dosimeter at various temperature.

4. Discussion

There are many advantages about nMAG gel. For example, nMAG could be prepared under normoxic (under 1 atmospheric), made various shape what the laboratory needs and no toxicity concerns. In addition, nMAG gel is able to regulate its content and gelatin concentration to change its response characteristics no matter for exposure or thermal reaction. Thermal therapy in clinic includes Interstitial Laser Ablation (ILA), Radiofrequency (RFA), Focused Ultrasound Ablation (or high-intensity focused ultrasound, HIFU), and Microwave Thermotherapy (14-16).

In previous research, We simply heated on nMAG gel dosimeters without radiation. The result of R_2 value is too small (<1.1) and changes within the range of 10% to poor temperature sensitivity (15,16).

In this experiment, we tried to give radiation dose uniformly to increase quantitative comonomers in gel dosimeters in order that more comonomers could decompose during heated. As a result, it is a method not only to enhance the R_2 upper limit but also to separate reactive value at each temperature. The higher dose we gave, the higher R_2 upper limit we obtained until over the saturation of nMAG gel dosimeters and upper limit (20 Gy). The result showed that no matter in which dose group, R^2 value is higher than 0.986. R_2 value of radiation dose more than 15 Gy is consistent and almost overlapping at higher than 40℃. This result represented that it is meaningless for getting no amount of radiation dose but it is obvious to separate dose which is caused by difference at 22-30℃ because of less influence on dissociation reaction (**Figure 3**). However, analyzing the standard deviation of each group, we could observe that the group in 50 Gy is significantly higher than other groups (**Figure 4**). This may be caused by thermal reaction because the gel dosimeters absorbed itself at high radiation dose, resulting in inaccuracy of subsequently heated reactions. In addition, the standard deviations of 5-20 Gy at over 44℃ are obviously higher than 30-44℃ ($p<0.001$) because gel is increasingly diffusing itself when heated at higher temperature range, or even dissolving the reaction lead to errors.

nMAG gel dosimeters is poorly sensitive to temperature without radiation. nMAG gel dosimeters enhance the range of thermal reaction and sensitivity because R_2 value enhances. The upper limit radiation dose detector of nMAG gel dosimeters are about 50Gy but R_2 value changes slowly treated with 20 Gy. The optimal range is lower about 20 Gy (12-14). Our experiments also showed that it could provide stable thermal reaction treated with lower 20 Gy and have the lower standard deviation.

Dose rate is one of the factors which affect R_2 value. Related research showed that R_2 value would fall on higher dose rate and the quantitative comonomers become less at the same radiation dose during exposure time. Treated with 100 (cGy/min) in 6MV x-ray beam could get the stable initial R_2 value (before heating) (14,17).

Should I measure initial R_2 value before heating to compare it? It may be cause another influence. Hayashi et al. showed that it is occurred that warming phenomenon during irradiation and MRI measurement18. Take treated with 100 (cGy/min) in 6MV x-ray beam as an example, the tube temperature rises about 2-4℃. If treated with 50 Gy, the temperature rises more than 6 ℃. This phenomenon

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could explain why the standard deviation significantly increased in 50 Gy group. Vandecasteele et al. found that the possible temperature rise in the samples is 1.5℃ to 2℃ after 1 to 2 hours MRI scanning (19). Recent studies have suggested that MR scanning of polymer gel dosimeters should be performed in a water container to stabilize the temperature within 0.2℃. In our study, the MRI scanning was performed in the water container, and the duration of each MRI scanning was 31 min. For this reason, the possible temperature rise in the samples should be under 0.5℃.

Warming phenomenon during radiation dose could eliminate differences because following up low temperature for 24 hours. R_2 value also keeps linear relationship. It is difficult to control warming phenomenon during MRI scanning so omitting initial R_2 measurement in this study to prevent errors.

There are some effects during MR scanning including scanning room temperature, pulse sequence parameters, coils and uniformity magnet and so on. It is primarily based on sensitivity of thermal reaction for sure. The spatial resolution is not taken into account. In second experiment, we reduce scan section and enhance twice scan thickness in order to enhance signal to noise ratio and decrease the scan time (scan time of first experiment is 48 min and scan time of second experiment is 31 min). In addition to reduce warming degree during the scan while scanning thick section will reduce magnetic field inhomogeneity (20).

We observed that standard deviation increased in 46-60℃ because the gel itself started to thermal dissolution and increase diffusion phenomenon. Literature pointed out that nMAG gel dosimeters melting point is about 60℃. It is close to gelatin concentration. Higher concentration can increase the melting point of gelatin. One research also pointed out that the gelatin content also has a great effect on the thermal absorption(18). 8% gelatin is a suitable concentration for measuring radiation doses in this study. The influences of thermal reaction sensitivity and accuracy on different gelatin concentrations consider to be discussed in the future.

Gelatin what we used is mammalian gelatin and cellulose can be added to change the gel strength and melting point. For example, HPMC is the derivative cellulose with thermo-reversible property. HPMC is soluble in cold water. When the HPMC solution is heated, a gel structure will form. Flocculation results from the weakening of hydrogen bonding between polymer and water molecules and the strengthening of interactions between polymer chains. Reducing temperature restored the HPMC solution to its original form. The gelling of combinative gels could be found both at the temperature lower than 25℃ and higher than 60℃. This result illustrated that the mammalian gelatin and HPMC still remain their cold and thermal gelation properties, respectively, after combination (21,22).

5. Conclusions

The experiment established that nMAG gel dosimeters have a good linear response for thermal change ranging from 22-60℃ after radiation. We also estimate 10-15Gy is a better choice to irritate because excessive dose causes the warming phenomenon on gel. The range of R_2 value has great variation in order to achieve good thermal responsiveness. It can improve the heating method in the experiment and discuss the spatial resolution parameters in detail to achieve demands of quality assurance testing in thermal surgery in the future.

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