



Technical note

Quantitative magnetic resonance elastography for polymer-gel dosimetry phantoms

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ARTICLE INFO

Article history:

Received 6 June 2018

Revised 3 December 2018

Accepted 10 February 2019

Keywords:

Polymer-gel dosimetry phantoms

Dynamic elastic properties

Shear modulus

Elastograms

Magnetic resonance elastography

ABSTRACT

Commonly dose-responses of conventional dosimetric methods are affected by a saturation dose and are known to be limited when the delivered dose is relatively high. In contrast, elastic properties of polymer-gel dosimeter phantoms play major roles in a new dosimetry technique using magnetic resonance elastography (MRE). A single volume of polymer-gel dosimeter solution containing methacrylic and ascorbic acid in gelatin initiated by copper was prepared. The material was subsequently stored in cylindrical containers for future use as a biological tissue-mimicking phantom material. The phantom material was irradiated with gamma rays, where absorbed doses of 10–50 Gy were delivered. To study the dynamic elastic behaviour, periodic mechanical external forces of 100–400 Hz were applied to generate shear waves in the samples. The radiation-induced changes in the shear modulus of the samples were estimated from wave-displacement images and converted to elastograms. The smallest and largest shear modulus values were approximately 2.10 ± 0.64 and 35.26 ± 2.85 kPa, respectively. The dynamic elastic response of the polymer-gel dosimeters showed an increased dependency with frequency. A linear relationship ($R^2 = 0.996$) was observed between the integrated area and the absorbed dose of the samples. The elastograms clearly showed that the largest shear modulus values were in the irradiated region of the polymer-gel dosimeter phantoms. Quantitative values of the shear modulus of polymer-gel dosimeters were estimated using MRE.

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1. Introduction

Medical procedures involving radiation therapy (radiotherapy), such as intensity-modulated radiotherapy (IMRT) [1–3] and surgical planning (stereotactic radiosurgery) [4–6], use sophisticated equipment. These techniques require rigorous quality control over the dose to be delivered to the patient [7]. This dose-distribution complexity means that it is crucial to use a dosimeter device capable of probing absorbed doses in volumetric form. Radiotherapy treatment planning usually involves the use of three-dimensional (3D) medical imaging [8]. Polymer-gel dosimeters can be designed to mimic the mechanical properties of soft biological tissue and can be prepared in any geometry [9]. The methacrylic and ascorbic acid in gelatin initiated by copper (MAGIC)-based gel dosimeter is one the most popular dosimeters due to its simplistic design and preparation [10,11]. Thus, it can be used to perform accurate measurement of 3D dose distributions [12]. Many approaches based

on imaging modalities are used to investigate gel dosimetry and map the absorbed dose distribution, including optical scanning [13], X-ray CT scanning [14], magnetic resonance relaxation-time imaging [15] and US [16,17]. Optical CT scanning is a good option when cost is an issue. This technique uses the optical attenuation coefficient as a parameter to correlate changes in this coefficient with the absorbed dose; however, the proportionality between them is only suitable under certain dose-limited conditions. X-ray CT uses the linear attenuation coefficient and gel density changes as parameters to be associated with absorbed dose. Some positive characteristics of this technique include its insensitivity to temperature and its intrabatch reproducibility; however, it is largely influenced by image noise generated by the tube voltage, which affects the dose resolution of the X-ray CT gel dosimetry. Relaxation-time imaging is the most popular imaging technique for collecting polymer-gel dosimetry data. The most commonly-used contrast is based on spin-spin relaxation rate to acquire quantitative R2 maps. Moreover, changes induced by radiation can affect the mechanical properties of polymer-gel dosimeters which alter the rigidity of the materials [18]. The dependency of radiation dose and mechanical properties (i.e. the elastic modulus), which

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are related to the acoustic speed of propagation in a medium, was first studied by US [16,17]. Similarly, a potential magnetic resonance-based imaging technique called magnetic resonance elastography (MRE) was proposed [19,20]. It is an efficient tool for accurately estimating the shear modulus in tissue samples [20–24]. Thus, mechanical parameters (i.e. the shear modulus) may be more sensitive indicators of the absorbed radiation dose than other conventional imaging parameters [25]; for example, the contrast in US images is directly related to the bulk modulus, the most relevant physical parameter related to contrast in CT is the linear X-ray attenuation coefficient and the contrast in MRI is defined by the longitudinal (T1) and transverse (T2) relaxation times of the biological tissues. For these imaging modalities, the range of variation of such physical parameters is significantly less than one order of magnitude [14,16,26]. Conversely, two-to-three orders of magnitude can be reached when considering shear modulus as the physical parameter responsible for imaging contrast [18,27].

Trade-offs of the commonly-used techniques are that: (i) the poor resolution in the off-axial direction, which is inherent to US imaging, has limited the accurate quantification of elastic properties [28], (ii) apart from the specificities of each gel-dosimetry technique, a common point among them is the dosimetric response saturating at elevated doses (i.e. 30 Gy) [29,30], (iii) the high cost of magnetic resonance equipment restricts the use of the technique and (iv) it is necessary to buy an elastographic module for the magnetic resonance system to make the technique viable in a clinic.

This study proposed a method based on the relationship between absorbed dose radiation and shear stiffness, which was referred to as magnetic resonance elastodosimetry (MRED). Absorbed dose distributions and dynamic elastic behaviour was investigated using polymer-gel dosimeter phantoms with broad range of absorbed doses.

2. Material and methods

2.1. Dosimetry phantom preparation

A single volume of gelatin solution containing MAGIC polymer-gel was prepared as described elsewhere [10]. Gelatin powder (250 Bloom, Gelita®) was added to ultrapure deionised water at room temperature (25 °C) and mixed slowly for 10 min. The solution was subsequently heated to 50 °C until a clear and homogeneous solution was obtained. The hot plate was turned off and the system allowed to cool down; however, the mixer remained switched on to maintain the homogeneity of the solution. Methacrylic acid (Acros®), ascorbic acid (Vetec®), copper sulphate (Vetec®) and formaldehyde (Acros®) were added at a temperature of 35 °C, as described elsewhere [9,31]. The gel was stored in an enclosed cylindrical plastic container (radius \times height = 45 \times 50 mm).

2.2. Phantom irradiation procedure

Five polymer-gel dosimetry phantoms were irradiated with doses ranging from 10 to 50 Gy using a conventional Cobalt-60 photon beam from a Theratron 780C unit (MDS Nordion, Kanata, Canada). Another phantom was not irradiated and was kept as a reference phantom. The source surface distance was 800 mm. A collimator size of 30 \times 30 mm² was chosen to produce the irradiated volume on the phantoms. Only the central part was exposed to the radiation, and the surrounding area was protected from radiation. Parallel-opposed fields (180°) were used to guarantee dose-distribution homogeneity within the volume.

2.3. MRR theory, image acquisition and processing

A conventional single-spin echo was used to obtain quantitative R2 maps [3,32]. By changing the echo time (TE), the T2 weighting in the base images can be varied [33]. The R2 value in each pixel can be calculated from two differently-weighted T2 images according to [15].

A double-echo spin-echo sequence with a short TE (20 and 100 ms) and a long repetition time (TR=4000 ms) was used [34]. The field of view (FOV) was 16 cm, the acquisition matrix size was 256 \times 256 pixels, the slice thickness was 2 mm and the acquisition time to obtain a slice was 2.50 min, as described elsewhere [10,33,35].

The mean R2 value was estimated by selecting a region of interest on the entire image of the polymer-gel dosimeter [3].

2.4. MRE theory, image acquisition and processing

In MRE, the generation of mechanical shear waves inside a sample is an important step and can be achieved using an electromechanical actuator coupled to the material. In this study, MRE experiments were performed using an electromechanical actuator, as a source of sinusoidal external excitation force of a single frequency, coupled to the polymer-gel dosimeters, as described elsewhere [20].

Shear waves, with frequencies ranging from 100 to 400 Hz, were induced by the electromechanical actuator applied to the top of the sample in a steady-state regime. The magnetic resonance scanning parameters used were FOV = 160 mm, TE = 26 ms, TR = 52 ms, acquisition matrix = 256 \times 256, slice thickness = 2.0 mm, flip angle = 30°, phase offsets = 4, frequency encoding direction = superior–inferior and acquisition time = 45 s.

The shear stiffness of the samples was estimated from wave propagation displacement images via an algorithm described elsewhere [36,37].

3. Results and discussions

To verify the absorbed dose distributions, elastograms were compared to relaxation maps obtained by MRI, as depicted in Figure 1. The left side of the figure shows the shear wave propagation images from the MRE experiments, while the middle column shows the elastograms of the entire phantoms. In these images, the surrounding region (radiation-free) and the irradiated area can be easily observed due to wavelength variation. The right panel showed a set of spin-spin relaxation-rate images. For all driving frequencies from 100 to 400 Hz, the MRE displacement images of the polymer-gel dosimeters showed wave-pattern variations.

The variation in shear stiffness with frequency in polymer-gel dosimeters is shown in Figure 2.

The data were fitted using a monoexponential fit. The sensitivities were found to be between 5.64 ± 0.23 and 36.74 ± 0.28 kPaGy⁻¹ for phantoms of 20 and 40 Gy, respectively, and the correlation coefficients were >0.999. The mean sensitivity was 15.10 ± 0.37 kPaGy⁻¹. The best correlation coefficient was found for the gel dosimeter phantom of 10 Gy ($R^2 = 1.000$). The sensitivity of the 'quasi-linear' low-dose region (0–10 Gy) ranged from 86.03 ± 0.14 to 15.75 ± 0.18 kPa.Gy⁻¹.

In quantitative analysis (i.e. dosimetry), calibration curves are often used to estimate the level of absorbed dose of a sample. The area under each curve in Figure 2 was computed by integration at a frequency of 100–400 Hz. The estimated areas of each shear modulus curve were subsequently obtained by subtracting the value of A_n , which was the shear modulus of the irradiated samples (10, 20, 30, 40 and 50 Gy), from A_0 , which was the shear

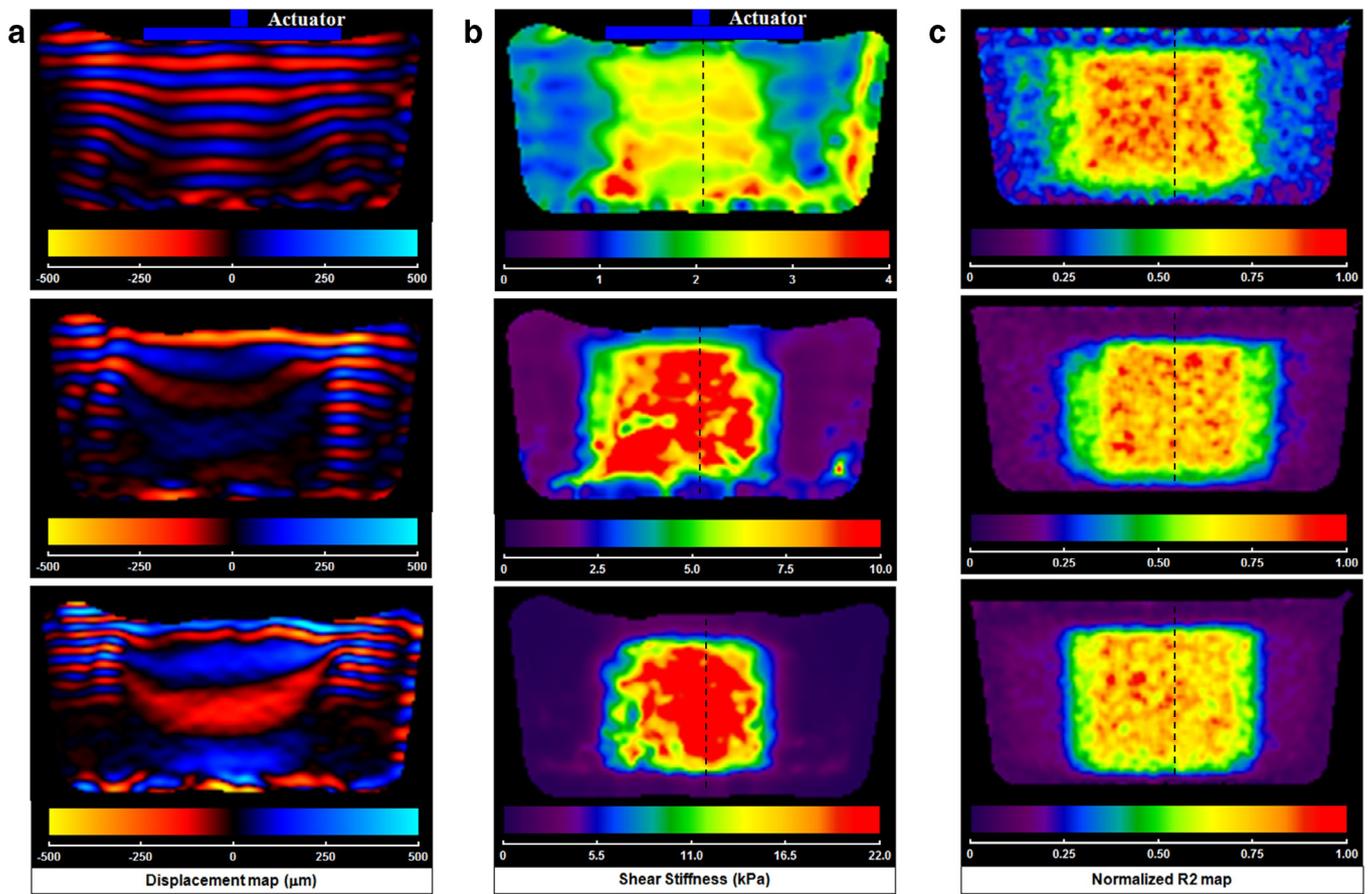


Figure 1. (a) Wave patterns of three polymer-gel dosimeters with varying absorbed doses (10, 30 and 50 Gy), where wavelength lengthening in the stiff region is easily visible. (b) A shear stiffness map estimated from the previous displacement maps of the absorbed dose dosimeters, clearly showing the stiff irradiated region. (c) The normalised magnetic resonance transversal relaxation rate image.

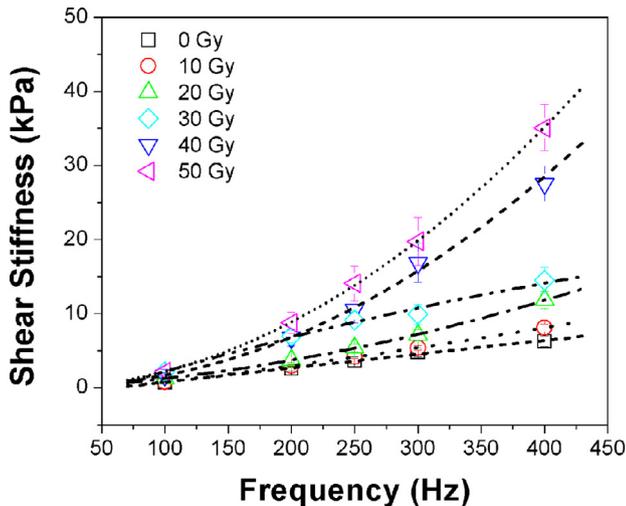


Figure 2. Shear stiffness of polymer-gel dosimeters measured by MRE as a function of five different frequencies: 100, 200, 250, 300 and 400 Hz.

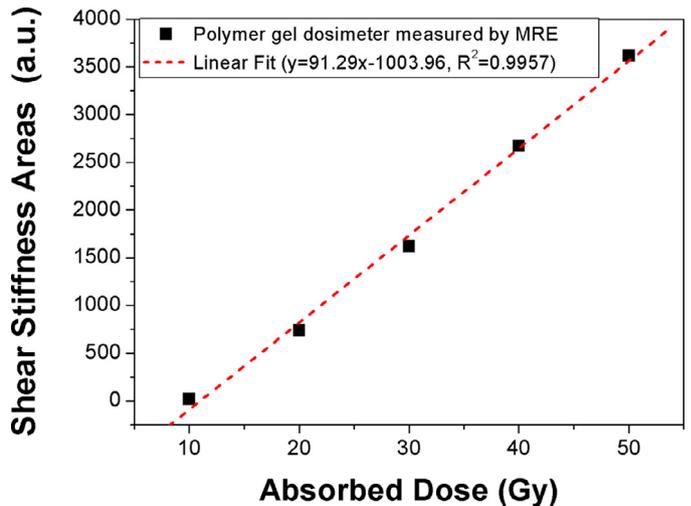


Figure 3. Shear stiffness area versus absorbed dose for all frequencies in polymer-gel dosimeter samples irradiated with 10–50 Gy.

modulus of the nonirradiated sample (0 Gy). Therefore five integral area values were achieved and used to evaluate sensitivity. A linear fit was applied to the data. Sensitivity was defined as the ratio between the shear modulus area ($A_n - A_0$) and the absorbed dose for the specific frequency range. As a result, a linear response ($R^2 = 0.996$) with absorbed dose was observed, as depicted in Figure 3.

The dynamic elastic behaviour represented by the mean shear stiffness of the dosimeter phantoms showed growth dependency as a function of excitation frequency. By fitting a line to the data, it was shown that the mean shear stiffness (integral area) increased systematically with increasing absorbed doses, with a correlation of $R^2 > 0.996$ for absorbed doses up to 50 Gy. A much better mechanical response was achieved using an excitation frequency of 300 Hz.

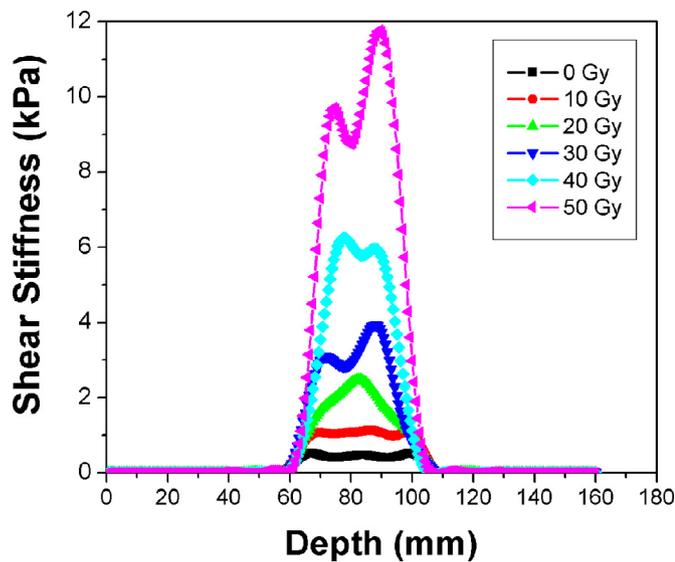


Figure 4. Shear stiffness profiles obtained from magnetic resonance elastograms, extracted from Figure 1b.

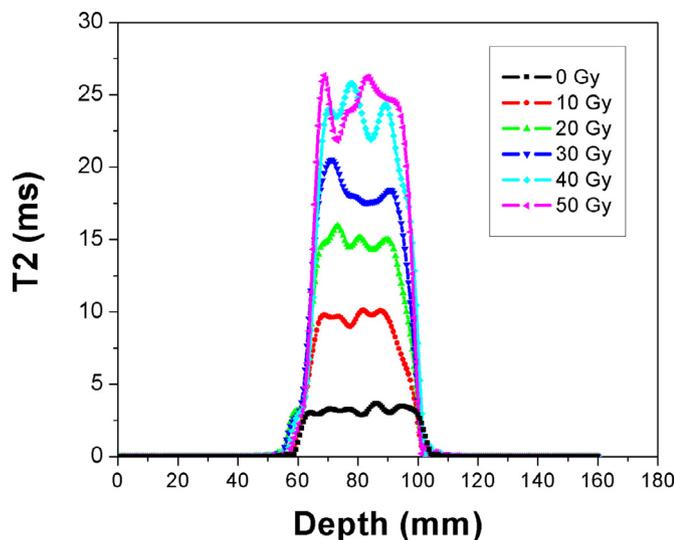


Figure 5. The spin-spin relaxation-time profiles from MRI relaxation rate maps, extracted from Figure 1c.

The profiles depicted in Figures 4 and 5 were drawn from a central line of interest in the images in Figure 1. The shear stiffness profiles obtained from magnetic resonance elastograms are illustrated in Figure 4.

The shear stiffness curves, dependant on the delivery doses that are directly related to the image contrast. The bottom profile shows the shear stiffness found in the control (nonirradiated) sample. The samples were subsequently exposed to absorbed doses of 10–50 Gy. Hence, the image contrast based on elastic modulus was more significant as the absorbed dose increased.

The spin-spin relaxation-time profiles from MRI relaxation rate ($R2=1/T2$) maps are shown in Figure 5.

In the irradiated region, the elasticity and T2 relaxation rate were affected by the gel polymerisation produced by the radiation beam. During irradiation-induced polymerisation, monomers of the polymer tend to aggregate. In such media, the spin-spin interaction of the protons decreased, which led to a reduction of T2 values. However, this phenomenon benefits the gel stiffness, which increases proportionally with the absorbed dose. MRE

provides sensitivity with the changing mechanical properties of the gel dosimeter, which can achieve signals with over two-to-three orders of magnitude, compared to the R2 relaxation rate.

As stated, quantitative analysis plays major role in dosimetry, where calibration curves, like Figure 3 are often used to estimate absorbed dose. For this, the response of the system must be known. In this investigation, the response of the system was the shear modulus. By establishing the relationship between shear modulus area (A) under the curve and absorbed dose (D), a response factor (RF) can be determined. The RF is proportionality constant for each dose and is simply the absorbed dose divided by the shear modulus area ($RF=D/A$). If samples containing known absorbed doses are evaluated as a function of excitation frequencies, the curve area can be measured to determine the RF. This process is referred to as a calibration. The response can be displayed on a graph where the x-axis is absorbed dose and the y-axis is the shear modulus curve area. Therefore the RF is simply the angular coefficient or sensitivity of the fitted curve. Thus, the method present here is based on the relationship between absorbed dose radiation and shear stiffness, which was referred to as magnetic resonance elastodosimetry (MRED).

4. Conclusions

Around the world, MRI has become a popular imaging technique that can be incorporated by almost all hospitals and clinics in their planning workflows to treat illnesses through radiation. The results obtained in this study demonstrate that MRE can be used to estimate shear stiffness and dose distributions in polymer-gel dosimeters. Magnetic resonance elastodosimetry (MRED) would be beneficial as a complementary technique to conventional dosimetry for measuring absorbed doses. MRED may be beneficial due to its better performance at radiation levels commonly used in radiotherapy and stereotactic radiosurgery treatments. It may play a major role in a new dosimetry investigation technique by providing accurate information regarding dose quantification based on shear stiffness.

Conflict of interest

The authors have no conflicts of interest.

Funding

This research was partially supported by two Brazilian research agencies: CNPq and CAPES.

Ethical approval

Not required.

Acknowledgement

The authors would like to express gratitude to Juliana Fernandes and Yogesh K. Mariappan for experimental assistance. Special thanks to Prof. Mostafa Fatemi (Ultrasound Research Laboratory), Dr Richard L. Ehman (MRI Research Laboratory) and the Department of Physiology and Biomedical Engineering at Mayo Clinic College of Medicine, Rochester, Minnesota, US.

References

- [1] Gustavsson H, Karlsson A, Back SA, Olsson LE, Haraldsson P, Engstrom P, et al. MAGIC-type polymer gel for three-dimensional dosimetry: intensity-modulated radiation therapy verification. *Med Phys* 2003;30:1264–71.

- [2] Vergote K, De Deene Y, Duthoy W, De Gerssem W, De Neve W, Achten E, et al. Validation and application of polymer gel dosimetry for the dose verification of an intensity-modulated arc therapy (IMAT) treatment. *Phys Med Biol* 2004;49:287–305.
- [3] Pavoni JF, Pike TL, Snow J, DeWerd L, Baffa O. Tomotherapy dose distribution verification using MAGIC-f polymer gel dosimetry. *Med Phys* 2012;39:2877–84.
- [4] Ruge MI, Kocher M, Maarouf M, Hamisch C, Treuer H, Voges J, et al. Comparison of stereotactic brachytherapy (125 iodine seeds) with stereotactic radiosurgery (LINAC) for the treatment of singular cerebral metastases. *Strahlenther Onkol* 2011;187:7–14.
- [5] Baldock C, De Deene Y, Doran S, Ibbott G, Jirasek A, Lepage M, et al. Polymer gel dosimetry. *Phys Med Biol* 2010;55:R1–63.
- [6] Gopishankar N, Watanabe Y, Subbiah V. MRI-based polymer gel dosimetry for validating plans with multiple matrices in Gamma Knife stereotactic radiosurgery. *J Appl Clin Med Phys* 2011;12:3333.
- [7] Silveira MA, Pavoni JF, Baffa O. Three-dimensional quality assurance of IMRT prostate plans using gel dosimetry. *Phys Med* 2017;34:1–6.
- [8] Watanabe Y, Mooij R, Perera GM, Maryanski MJ. Heterogeneity phantoms for visualization of 3D dose distributions by MRI-based polymer gel dosimetry. *Med Phys* 2004;31:975–84.
- [9] Watanabe Y, Warmington L, Gopishankar N. Three-dimensional radiation dosimetry using polymer gel and solid radiochromic polymer: from basics to clinical applications. *World J Radiol* 2017;9:112–25.
- [10] Fernandes JP, Pastorello BF, de Araujo DB, Baffa O. Formaldehyde increases MAGIC gel dosimeter melting point and sensitivity. *Phys Med Biol* 2008;53:53–8.
- [11] Fong PM, Keil DC, Does MD, Gore JC. Polymer gels for magnetic resonance imaging of radiation dose distributions at normal room atmosphere. *Phys Med Biol* 2001;46:3105–13.
- [12] De Deene Y, De Wagter C, Van Duyse B, Derycke S, De Neve W, Achten E. Three-dimensional dosimetry using polymer gel and magnetic resonance imaging applied to the verification of conformal radiation therapy in head-and-neck cancer. *Radiother Oncol* 1998;48:283–91.
- [13] Oldham M. Optical-CT scanning of polymer gels. *J Phys* 2004;3:122–35.
- [14] Sellakumar P, Samuel EJJ. Study on energy dependence of PAGAT polymer gel dosimeter evaluated using X-Ray CT. *Radiat Meas* 2010;45:92–7.
- [15] Maryanski MJ, Schulz RJ, Ibbott GS, Gatenby JC, Xie J, Horton D, et al. Magnetic-resonance-imaging of radiation-dose distributions using a polymer-gel dosimeter. *Phys Med Biol* 1994;39:1437–55.
- [16] Mather ML, Whittaker AK, Baldock C. Ultrasound evaluation of polymer gel dosimeters. *Phys Med Biol* 2002;47:1449–58.
- [17] Crescenti RA, Bamber JC, Oberai AA, Barbone PE, Richter JP, Rivas C, et al. Quantitative ultrasonic elastography for gel dosimetry. *Ultrasound Med Biol* 2010;36:268–75.
- [18] Mather ML, De Deene Y, Whittaker AK, Simon GP, Rutgers R, Baldock C. Investigation of ultrasonic properties of PAG and MAGIC polymer gel dosimeters. *Phys Med Biol* 2002;47:4397–409.
- [19] Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic-resonance elastography by direct visualization of propagating acoustic strain waves. *Science* 1995;269:1854–7.
- [20] Mariappan YK, Glaser KJ, Ehman RL. Magnetic resonance elastography: a review. *Clin Anat* 2010;23:497–511.
- [21] Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. *Clin Gastroenterol Hepatol* 2007;5:1207–13 e2.
- [22] Kemper J, Sinkus R, Lorenzen J, Nolte-Ernsting C, Stork A, Adam G. MR elastography of the prostate: initial in-vivo application. *Rofo-Fortschr Rontg* 2004;176:1094–9.
- [23] Sack I, Beierbach B, Hamhaber U, Klatt D, Braun A. Non-invasive measurement of brain viscoelasticity using magnetic resonance elastography. *NMR Biomed* 2008;21:265–71.
- [24] Sinkus R, Tanter M, Xydeas T, Catheline S, Bercoff J, Fink M. Viscoelastic shear properties of in vivo breast lesions measured by MR elastography. *Magn Reson Imaging* 2005;23:159–65.
- [25] Low G, Kruse SA, Lomas DJ. General review of magnetic resonance elastography. *World J Radiol* 2016;8:59–72.
- [26] Deene YD. Review of quantitative MRI principles for gel dosimetry. *J Phys: Conf Ser* 2009;164(1):1–42.
- [27] Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound Med Biol* 1998;24:1419–35.
- [28] Parker KJ, Doyley MM, Rubens DJ. Imaging the elastic properties of tissue: the 20 year perspective. *Phys Med Biol* 2011;56:R1–R29.
- [29] Trapp JV, Michael G, de Deene Y, Baldock C. Attenuation of diagnostic energy photons by polymer gel dosimeters. *Phys Med Biol* 2002;47:4247–58.
- [30] Maryanski MJ, Audet C, Gore JC. Effects of crosslinking and temperature on the dose response of a BANG polymer gel dosimeter. *Phys Med Biol* 1997;42:303–11.
- [31] Madsen EL, Hobson MA, Shi HR, Varghese T, Frank GR. Tissue-mimicking agar/gelatin materials for use in heterogeneous elastography phantoms. *Phys Med Biol* 2005;50:5597–618.
- [32] Baldock C, De Deene Y, Doran S, Ibbott G, Jirasek A, Lepage M, et al. Topical review: polymer gel dosimetry. *Phys Med Biol* 2011;55:R1–R63.
- [33] Carneiro AAO, Vilela GR, de Araujo DB, Baffa O. MRI relaxometry: methods and applications. *Braz J Phys* 2006;36:9–15.
- [34] Deene YD. How to scan polymer gels with MRI? *J Phys: Conf Ser* 2010;250(1):1–10.
- [35] Murakami Y, Nakashima T, Watanabe Y, Akimitsu T, Matsuura K, Kenjo M, et al. Evaluation of the basic properties of the BANGkit gel dosimeter. *Phys Med Biol* 2007;52:2301–11.
- [36] Knutsson H, Westin CF, Granlund G. Local multiscale frequency and bandwidth estimation. In: *Proceedings of international conference on image processing, ICIP-94*, 1; 1994. p. 36–40.
- [37] Manduca A, Muthupillai R, Rossman PJ, Greenleaf JF, Ehman RL. Image processing for magnetic resonance elastography. *Med Imaging* 1996: *Image Process* 1996;2710:616–23.