Three-dimensional dosimetry using polymer gel and magnetic resonance imaging applied to the verification of conformal radiation therapy in head-and-neck cancer

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Abstract

Background and purpose: It was our aim to investigate NMR-based BANG gel dosimetry as a three-dimensional dosimetry technique in conformal radiotherapy.

Materials and methods: The BANG gel consisting of gelatin, water and co-monomers was first validated in a cylindrical glass flask for a single standard beam. Next, the gel contained in a human neck-shaped cast was used to verify a treatment plan for the conformal irradiation of a concave tumour in the lower neck. Magnetic resonance relaxation rate images were acquired and, based on an appropriate calibration of the gel, converted to absorbed dose distributions. The resulting maps were compared with dose distributions measured using radiographic film.

Results: The gel-measured dose profiles of standard beams agreed within 3% (root mean square difference) with the profiles measured with high spatial resolution by a diamond detector. For the multi-beam conformal treatment, the difference map between gel-measured and film-measured dose distributions revealed a noise component and a more systematic deviation including structural or space-coherent patterns. The mean absolute value of the difference amounted to 8%. A number of possible causes for this deviation are designated.

Conclusions: Polymer gel dosimetry in combination with magnetic resonance imaging is a promising method for dosimetric verification of conformal radiotherapy. © 1998 Elsevier Science Ireland Ltd. All rights reserved

Keywords: 3D gel dosimetry; Conformal radiotherapy; Head-and-neck cancer; Polymer gel; Intensity modulation

1. Introduction

At least two types of radiation sensitive gels are being investigated in the context of radiotherapy by several groups: Fricke gel and BANG gel.

Fricke gel is basically an agarose gel that contains ferrous sulphate [2,3,7,11,13,14,16,22–24,26,30–32]. Irradiation of the Fricke gel causes a set of chain redox reactions resulting in the oxidation of ferrous ions. This ionic reaction results in a change of the nuclear magnetic spin-lattice relaxation time, T1 [9,26]. The major disadvantage of the Fricke gel however is the diffusion of the ferric and ferrous ions, resulting in blurring and loss of spatial accuracy [25].

A second type of gel, the BANG gel, was proposed by Maryanski et al. [19–21] and consists of a gelatin gel in which monomers are dissolved. By radiation, the co-monomers polymerise to cross-linked polyacrylamide, resulting in a change of the nuclear magnetic spin-spin relaxation time T2. This kind of gel displays a more stable behaviour with respect to the diffusion as the polymer structures remain fixed.

The ultimate purpose of this investigation is to assess the applicability of the BANG gel for the verification of con-
formal radiotherapy treatment plans. The central idea behind conformal radiotherapy is to tailor and confine the high-dose volume to the planning target volume. This allows the enhancement of the absorbed dose in the tumour while limiting radiation in the surrounding structures. Conformal radiotherapy promises a significant improvement of local control and palliation. Beam intensity modulation is a flexible tool in conformal radiotherapy to actively control both the high-dose distribution and the protection of organs at risk. One method of beam intensity modulation is to decompose the beams into beam segments which are delivered sequentially in a static mode [5,6]. This paper deals with the preclinical verification of a treatment plan that uses static beam intensity modulation to irradiate a concave tumour in the lower neck. The plan was specifically designed for the geometry of the Rando phantom (Alderson Research Laboratories, Stamford, CT).

2. Materials and methods

2.1. Gel production

Acrylamide (3%(w/w)) and \(N,N'\)-methylene-bis-acrylamide (3% (w/w)) are dissolved in a gel composed of gelatin and water [19–21]. Both monomers are obtained from Sigma–Aldrich (Bornem, Belgium) and are of electrophoresis grade. Because of the large amount of the cross-linking agent, \(N,N'\)-methylene-bis-acrylamide, three-dimensional polymer networks are formed during irradiation. It is believed that these polymer networks consist of small spherical aggregates [17]. The higher the absorbed dose, the higher the number of polymer aggregates that are formed. The polymer aggregates are not able to diffuse through the gel matrix. The chemical propagation reaction only takes place very locally at the site of chemical initiation.

The gelatin (Bloom 300/pig skin) was fabricated by Systems Bioindustries Benelux (Brussels, Belgium) [29].

We have assessed the soft-tissue equivalence of the BANG gel theoretically by calculating the mean electron density and the effective atomic number [15]. As a result, the effective atomic number and the electron density of the BANG gel compared with water as 0.987 and 1.028, respectively.

To produce the gel, we divide the amount of water into two equal parts in which the monomers and gelatin are dissolved respectively. To dissolve the cross-linking agent, we heat the solution to about 50°C. We dissolve the gelatin in cold water after which the gelatin swells. Thereafter, the gelatin solution is heated to 45°C, the temperature at which there is a gel-to-sol transition. Subsequently, both solutions are cooled down to 30°C before mixing.

All processing steps are completed in one set-up containing interconnected air tight reaction flasks which are bubbled by nitrogen to expel oxygen as oxygen would inhibit the polymerisation reaction during irradiation [19]. The set-up is further equipped with temperature and oxygen meters (type Cellox 325 from WTW, Weilheim, Germany) and a peristaltic pump (type Watson Marlow, Falmouth, Cornwall, UK). The pump was provided with flexible Tygothane tubing (Norton S.A., Performance Plastics, Akron, OH).

The definitive gel is pumped over into a glass recipient or human shaped PVC cast placed in a glove box. This perspex box is also flushed with nitrogen in order to keep the oxygen concentration lower than 0.03 mg/l. At the final stage, the oxygen level in the gel is less than 0.01 mg/l. The resulting gel phantom is sealed and placed in a refrigerator which, in case of a cast, is being flushed with nitrogen in order to confine permeation of oxygen through the cast. The oxygen level in the refrigerator was kept for one day below 3 mg/l, which is one third of the oxygen concentration under standard temperature pressure (STP) conditions. The permeability of PVC for oxygen is in the range \(10^{-12} \text{–} 10^{-10} \text{cm.mm.}(s.cmHg)^{-1} \) [28]. Further characteristics of the PVC material used are given in Section 2.5.

2.2. Irradiation and magnetic resonance imaging (MRI)

Most gel dosimeters were irradiated in a 5-MV photon beam produced by a linear accelerator (Elekta/Philips SL 75–5). Only the human shaped gel phantom was treated with 6 MV photons from a dual energy linear accelerator (Elekta/Philips SL25) equipped with a multileaf collimator. Each gel dosimeter was positioned on the treatment couch by aligning the transverse, sagittal and coronal marks with the respective laser lines. Unless otherwise specified, we exposed the gels to a nominal dose of 10 Gy at a rate of about 3.6 Gy/min. In the MR-scanner, the dosimeter was positioned using the light lines of the scanner allowing the orientation and longitudinal position to be replicated. After MR-acquisition we conducted a translation in the transversal plane in order to obtain an accurate match to the CT-images used for dose planning. This operation was guided visually without computer optimisation.

Each gel dosimeter was placed in the clinical MR-scanner (Magnetom, SP, 1.5 T, Siemens, Erlangen, Germany) for one night prior to scanning in order to stabilise and homogenise temperature. From previous experience we know that, while scanning the gel, the temperature in the dosimeter remains constant and uniform at 21.2°C within 0.5°C. Most gels were scanned in the body coil except for the test tubes which were placed in the head coil. We used a multiple spin-echo sequence that performs 32 echoes. The echoes were equally separated by 50 ms. A phase-alternating phase-shift (PHAPS) encoding scheme was applied to compensate for ghosting and mirror artefacts due to stimulated echoes [10]. A repetition time of 5 s was used to ensure total T1-relaxation for each phase line. The slice thickness of the images was 5 mm and the field of view was 400 mm. The other sequence parameters were MS/NEX = 256/1.
resulting in a voxel size of \((1.56 \text{ mm} \times 1.56 \text{ mm} \times 5 \text{ mm})\). The total acquisition time for an R2-image, where \(R2 = (T2)^{-1}\), was 42 min.

It is well known that a multiple spin-echo sequence does not provide the true T2-values. However, there is much evidence that the apparent T2-values obtained by the multiple spin-echo sequence linearly correlate with the true T2-values \([1,4,8,18,35]\). The calibration procedures reported further are based on the link between the apparent T2 to the absorbed dose. We transfer the set of 32 differently T2-weighted base images to a workstation (DEC station 5000/200, Digital) on which the R2-images are computed. The R2 relaxation rate of each pixel is retrieved by fitting the intensity of the pixel in the consecutive base images to a monoeponential decay applying a \(\chi\)-square minimisation based on the Levenberg-Marquardt algorithm \([27]\). The resulting R2-image is converted to the dose distribution using the calibration curve described in the Section 2.3.

2.3. Detailed study of dose-response of the gel

Initially, we determined the dose-response of each gel batch by exposing ten test tubes containing gel to different known doses. Each tube was irradiated separately in a cubic water tank \((22 \text{ cm} \times 22 \text{ cm} \times 22 \text{ cm})\) at a depth of 5 cm and with its axis perpendicular to the beam axis.

During MR-scanning, the ten test tubes were placed in a cylindrical recipient through which water was pumped from a thermostatic bath in order to stabilise and homogenise the temperature. The gel temperature in the test tubes was measured during the image acquisition using six fibre-optic probes and a fluoroptic thermometer (Luxtrom, Santa Clara, CA).

By linear regression of R2 on dose we obtain the calibration curve for the specific gel temperature. To investigate the temperature dependence of the dose response, the temperature of the circulating water was varied. R2-images were recorded not before the temperature in the test tubes equalled the temperature of the circulating water.

Although the above described procedure using the test tubes allows to study the dose response of the gel, two problems emerge when applying the method to calibrate the gel for dosimetry. First, for lack of room in the MR-scanner the imaging acquisition of the actual gel dosimeter has to be done separately from the imaging of the test tubes. This factor complicates the calibration procedure and lets the temperature dependence undermine the accuracy. Secondly, the PVC cast seems to alter the dose response. Therefore, we worked out two calibration procedures that make only use of the gel dosimeter itself. In case of the standard beam, we retrieved the depth-R2 function and identified it with the known depth-dose function. For the verification of beam intensity modulation, we measured the dose in about ten points using thermoluminescent dosimeters (TLDs). This method is further outlined in Section 2.5.

2.4. Standard beam

A cylindrical glass flask containing gel was exposed to a square field having a size of 5 cm at isocentre. The source to surface distance (SSD) was 90 cm. The dose–R2 calibration curve was obtained in this case by fitting the central axis depth–R2 curve to the depth–dose curve that was measured in a separate experiment by scanning a 0.125 cm\(^3\) ionisation chamber (type 233642, PTW, Freiburg, Germany) in water. Cross-beam R2-images were taken at depths of 5 cm and 10 cm. The dose delivered at isocentre was 7.3 Gy. The profiles were compared with the profiles recorded with the 0.125 cm\(^3\) ionisation chamber and a diamond detector (serial no. 6–017, PTW, Freiburg, Germany) in a computerised scanning water phantom.

2.5. Beam intensity modulation

A treatment plan was designed for a concave target in the head-and-neck region of the anthropomorphic Rando phantom using the Gratis\textsuperscript{TM} planning system \([33]\). The virtual simulation was based on CT scans of Rando and the dose computation employs a 3D-differential scatter air ratio algorithm. Dose computations were performed without corrections for tissue-density heterogeneity so that the dose plan obtained was also applicable to the gel phantom. One of the challenges in the head and neck region is to confine the dose delivered to the spinal cord. The designed plan is based on a static beam segmentation technique and involves 20 beam segments spread over eight gantry angles plus two non-segmented wedged beams.

This technique allows us to clinically reach an in-target dose inhomogeneity lower than 25% and a minimum target dose of 70 Gy without exceeding 50 Gy in the spinal cord.

Fig. 1. (a) CT-based lateral topogram of the Rando phantom and cranial-caudal delineation of the beam in the case of 0° gantry angle. TLD and film dosimetry are performed in transverse cross-sections #1 and #2 (defined, respectively, between slabs 8–9 and 9–10). (b) CT-scan of cross-section #2 showing in white solid outline the hypothetical concave target that surrounds the spinal cord. Twenty beam segments of various widths and weight were spread over the eight gantry angles indicated. All beam segments had their medial edge tangential to the concavity around the spinal cord.
[6]. Also for this treatment of Rando, the segment weights were optimised heuristically. Fig. 1 gives the lay-out of both the treatment and dosimetric verification. The computed dose distribution was normalised by locating the normalisation point at the centre of gravity of the planning target volume. The treatment plan was verified by using film and polymer gel.

For film dosimetry, the Rando phantom itself was irradiated to a dose of 1 Gy at the normalisation point. Two radiographic films (Kodak X-OMAT V ready-pack) were put in cross-sections #1 and #2 respectively, as indicated in Fig. 1a. In addition to the films, TLDs were introduced in an appropriately selected subset of the holes pre-drilled in Rando. The TLDs had been individually calibrated previously and were of the type LiF TLD-100 (Harshaw) ribbon (1/8” × 1/8” × 0.035”). For gel dosimetry, a cast to hold the gel was made of 4-mm thick PVC plate (extruded Isopur, clear transparent, density 1.4 g/cm³). The cast was modelled after the neck region of the Rando phantom by thermoplastic vacuum moulding and was finally assembled using PVC glue. The gel phantom was irradiated a dose of 10 Gy at the normalisation point.

Each gel dosimeter was positioned on the treatment couch and aligned using the laser lights that mark the three orthogonal planes that contain the treatment unit isocentre. Therefore, both the Rando-phantom and the gel phantom had previously been provided with the lines.

3. Results and discussion

3.1. MR-image uniformity of not-irradiated gel

In an introducing experiment we assessed the image non-uniformities when scanning a homogeneous un-irradiated gel. We used two large glass cylindrical flasks of diameter (length) equal to 400 (120) mm and 130 (250) mm respectively. The sequence parameters were the same as for the imaging of irradiated gel except for the field of view which was 500 mm instead of 400 mm. We rated the uniformity as the standard deviation of R2 after it had been averaged over 10 × 10 pixels in order to suppress the random noise. We found the uniformity to be within 1% in any transverse slice of 5-mm thickness as well as in the longitudinal direction.

3.2. Detailed study of dose-response of gel

In the preliminary experiment involving the irradiation of gel-filled test tubes, we found a quasi-linear relation between absorbed dose and transverse relaxation rate R2 for doses lower than 10 Gy (Fig. 2a).

This argues for the linear regression we used to derive the R2-dose calibration curve. The dose-response however shows a significant dependence on the gel temperature during MR-imaging. We noticed a linear temperature dependence of both the slope and intercept of the dose-R2 calibration curve (Fig. 2b,c). This temperature dependence is in agreement with the Bloembergen–Purcell–Pound theory of nuclear spin relaxation in liquids and the Stokes’ relationship between viscosity and the rotational correlation time [34] in the temperature interval considered. We found a value $6.3 \times 10^{-3}$/s per °C for the temperature coefficient of the slope compared with $7.6 \times 10^{-3}$/s per °C measured by Maryanski et al. [21]. This difference might be attributed to a different composition of the gelatin, as we used the same quality of co-monomers.

3.3. Standard beam

Fig. 3a represents the depth-dose curve that was acquired with the ionisation chamber for the (5 cm × 5 cm) field. In the companion gel experiment, the depth–R2 curve was retrieved. A least squares fit allowed us to construct the linear dose–R2 calibration curve. The resulting depth–dose curve registered by gel is also depicted in Fig. 3a. The superficial dose could not be measured by gel as it was deposited in the basis of the glass cylindrical flask. Using the same dose-R2 calibration curve, we derived the gel-measured beam profiles in both X- and Y-direction. The profiles obtained with a scanning diamond detector in a water phantom are compared with the gel-measured ones in Fig. 3b–e. For each scanning direction, the diamond detector was mounted such that the spatial resolution was maximum (0.21 mm). The dose response of the diamond detector was correlated to the response of gel by comparing the magnitude of the diamond-measured depth-dose curve to that measured with the ionisation chamber for the purpose of gel calibration as described above. The minor deviations that can be detected in Fig. 3b,c are due to an over-response of the gel at the beam edges. This is attributed to diffusion of monomers from regions of high concentration to regions of depletion [21]. These monomers may then interact with long-living macro-radicals at the edge of a high-dose region. The root mean square difference between the profiles obtained with the two measuring techniques amount to 3% for the X-profiles and 2.5% for the Y-profiles. The over-response of the gel is only an issue in regions of high dose gradient such as the beam edges: about 1 Gy/mm and 0.5 Gy/mm at 5 cm and 10 cm depths, respectively. In the depth–dose curve, on the other hand, the dose gradient in the build-up is sufficiently low to warrant a linear dose response (Fig. 3a).

3.4. Beam intensity modulation

After photographic processing, the films were digitised using a Vidar VXR-12 system (Vidar Systems Corporation, Herndon, VA). The doses measured by the TLDs that accompanied the films were used to calibrate the dose response of the film. For the gel experiment we used the same TLD-measured doses after multiplication with a factor of 10. Only the TLD measurement obtained near the trachea...
of the Rando phantom was dropped. The respective calibration curves that resulted from a linear regression are plotted in Fig. 4a,b. The quite scarce dose sampling results from the fact that intermediate doses practically only occur in dose gradients where TLDs cannot be used (see for instance Fig. 5).

Notwithstanding the assumption that the film responds linearly from 0 to 1 Gy, the linear regression line practically always falls within the 5% error margin around the TLD-measured doses.

The slice thickness of the MR-images was 5 mm, providing a reasonable compromise between spatial resolution and signal to noise ratio (SNR). We determined the SNR by considering a region of interest of homogeneous dose response and by calculating the ratio of the mean value to the standard deviation of the pixel intensities. The SNR found was 165 in the base images and about 110 in the resulting R2-images.

The dose distributions obtained by gel and film dosimetry were put into the same image format for the two cross-sections studied (Fig. 5). For the purpose of comparison, the gel-measured doses were divided by a factor of ten. We
Fig. 3. Depth-dose curve and cross-beam profiles of a 5 cm × 5 cm field (5 MV, SSD = 90 cm, 0° collimator rotation angle). squares: polymer-gel; circles: point detector in automated water phantom (0.125 cm³ chamber in panel a, diamond detector in panels b–e). (a) Depth-dose curve along central axis. (b) Profile in X-direction at depth of 5 cm. (c) Profile in Y-direction at depth of 5 cm. (d) Profile in X-direction at depth of 10 cm. (e) Profile in Y-direction at depth of 10 cm.
observe that the 0.8-Gy isodose completely encloses the planning target volume. The ‘dose’ registered in air by film forces the 0.2-Gy isodose to leave the body outline.

In order to quantitatively compare gel and film dosimetry, we considered the percent absolute value of the difference (PAVD) between the dose maps obtained with gel dosimetry and obtained with film dosimetry:

$$\text{PAVD}(x,y) = \frac{200 \times |D_{\text{gel}}(x,y) - D_{\text{film}}(x,y)|}{D_{\text{gel}}(x,y) + D_{\text{film}}(x,y)}$$  \hspace{1cm} (1)$$

with $D_{\text{gel}}(x,y)$ and $D_{\text{film}}(x,y)$ the dose in pixel $(x,y)$ in the dose map obtained with gel and film dosimetry, respectively. In the resulting PAVD-images, shown in Fig. 6, it is observed that the PAVD show high values (>20%) in a border zone that is approximately 6 mm wide. This is attributed to an inhibition of the polymerisation near the wall of the recipient, probably caused by the release of oxygen initially adhered to the PVC cast. The mean PAVD in the images, excluding the border zone, amounts to 8% in both cross-sections. This mean PAVD is partly due to a systematic deviation between both dose distributions: the average of the gel-measured dose is 4% higher than the average of the film-measured one. In addition to random noise, the PAVD images further show spatial coherences: the beam outlines can still be recognised in both PAVD-images. This may be due to a geometrical mismatch of the images, the partial volume effect of MRI due to the slice thickness of 5 mm, and inaccuracies in the calibration of the film, i.e. the assumed linearity.

A further explanation is the fact that the gel phantom is homogeneous while the Rando phantom in which the radiographic films and the TLDs had been inserted contains a skeleton and a trachea. Therefore, we studied the absorbed dose in a circular shell around the spinal cord (Fig. 7) in cross-section #1. We averaged the gel- and film-measured dose over annular sectors of 1 degree defined between radii of 23 and 31 mm. The resulting course of dose displays maximum fluctuations of 35% common to both film and gel dosimetry. The fluctuations are angle-correlated and are clearly governed by the beam trajectories. The gel registers a higher dose at the position of the trachea.
4. Conclusions

Although the production and processing of polymer gel is both difficult and subtle, we obtained a radiation dose response similar to that published in the recent literature [12,19].

Polymer gel dosimetry in combination with MRI offers a unique potential to explore radiation dose distributions in three dimensions. The method we implemented has been validated for dosimetry of standard beams and for verification of a multibeam conformal treatment. In case of standard beams, the gel dosimeter corresponds quantitatively well with diamond detector. The root mean square difference between the dose profiles measured with the different methods remains within 3%. Part of the difference is due to an over-response of the gel in regions of high dose gradient.

For the in-toto verification of complex arrangements of beams, polymer-gel dosimetry applied in a human shaped phantom yields an unequalled tool. We applied the method to the dosimetric verification of a conformal treatment plan that was based on static beam segmentation. A quantitative comparison with film dosimetry performed on the same treatment plan revealed a problem of dose underregistration by the gel near the cast. Except for this border zone, the mean absolute value of the difference between the gel- and film-measured dose distributions amounted to 8%. This figure includes both random and systematic discrepancies which have been accounted for. A more quantitatively rigorous comparative study of gel and film dosimetry will be the subject of a forthcoming paper.

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