Iodine contrast nPAG for radiologically visible target region in deformable dosimeters

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Abstract. The utility of gel dosimeters is sought to be improved upon in this study which proposes a target region of different X-ray CT contrast that is dose sensitive. The changes in the physico-chemical makeup of nPAG caused by the addition of the X-ray imaging Iodine based contrast agent Isovue are explored. The impact of this change on dose measurements is also discussed. The increase in HU as it correlates with increasing Isovue concentration is detailed, along with the dosimetric changes that occur, namely the steepness of the dose response curve and general shape of the percentage depth dose curve. It is noted that diffusion of Isovue from one gel region to another has significant dosimetric impact and the experimental method was constructed and conducted with this in mind. Further refinement and optimisation of the Isovue nPAG formulation will lead to a target region dosimeter that can be contoured on X-ray CT and used in the improvement of planning protocols, especially in cases that involve motion and deformation of target volumes.

1. Introduction
Polymer gel dosimeters provide a valuable measurement tool for the assessment of 3D conformal radiotherapy [1], with the dose distribution that is delivered to a dosimeter being readily visible and resolvable within the volume [2]. The shape of the deposited dose in the volume is stable for a length of time and if the dosimeter moves or changes conformation this will be evident in the dose distribution visible in the dosimeter volume. The polymer gel is a material that is able to change shape while undergoing irradiation and still measure a spatially accurate dose distribution which has seen polymer gels used for the study of motion and deformation in radiotherapy [3]. The entire dosimeter volume is often considered as an irradiated volume, or a plan aligned and delivered to the dosimeter with that intent being to assess the agreement of the total dose delivered and localized variations investigated. The current generation of polymer gel dosimeters generally lacks any internal features that are resolvable visibly or by X-ray CT. Adding such a feature may offer a pathway for increasing the utility of gel dosimeters for treatment verification [4] by clearly allowing assessment of dose difference regions with respect to target boundaries.

By introducing a target into a gel dosimeter this ‘gel-in-gel’ geometry can simulate a target present within an irradiated volume. The inner gel can be treated as a target volume and this feature presents opportunities for bettering the assessment of motion and deformation using gel dosimeters. The role of a target region inside a gel dosimeter would be to benchmark and improve dose calculations, image
guidance, tracking strategies and setup strategies in treatments involving motion and deformation. This target volume is proposed to be comprised of nPAG containing an X-ray imaging contrast agent, namely Isovue. It is expected that due to the addition of Isovue in only a certain volume of the dosimeter a readily visible and imageable target region will be apparent.

The increase in the HU of nPAG due to adding Isovue is investigated, the intent being to provide a clearly visible and recognizable boundary in X-ray CT. From this study the working concentration of Isovue was identified. It is then logical to identify the dosimetric properties of the iodinated nPAG(InPAG), it’s dose response curve, dynamic range and depth dose behavior. The insertion or manufacture of the composite dosimeter is detailed and challenges with the production of target regions in gel dosimeters were also identified.

An investigation of several imaging and dosimetric properties of InPAG were undertaken with the intent of refining the formulation for optimal utility in the form of a deformable target region dosimeter. The visibility of the target region is considered vitally important for the dosimeter’s utility and the necessary concentration of Iodine contrast agent required for a well-defined target volume was observed to impact the dosimetric properties of the gel, which informed some decisions when optimizing the method laid out here.

2. Method

2.1. Iodine concentration required for X-ray contrast
The nPAG used in this study is the same formulation used by Yeo [5] and is composed of 6 % w/w gelatine (Type A from porcine skin, Sigma Aldrich Ltd., Oakville, Canada) for the hydrogel matrix. Dissolved in this matrix are 3 % w/w N,N’-methylene-bis-acrylamide (Bis) and 3 % w/w acrylamide (Aam)(both from Sigma Aldrich Ltd.). The remaining mass is DI water, with 0.01 mM hydroquinone and 5 mM of Bis[tetrakis(hydroxymethyl-phosphonium)]sulphate (THPS) added to combat autopolymerisation and atmospheric oxygen diffusion respectively. Iodine contrast agent Isovue 300 was added in concentrations of 0.37 %, 0.73 %, 1.47 % and 2.93 % w/w, replacing an equivalent mass of water. These various preparations were then scanned using a Phillips Brilliance Big Bore X-ray CT to determine a correlation between Iodine concentration and HU.

2.2. Dosimetric impact of Iodine
The impact on the dose response of the gel and how it has changed due to the addition of Isovue was investigated. The changes in the chemistry of the gel were examined as it relates to the measured dose response.

2.2.1. Dose response Calibration Curve
Dose response curves for 0.5 %, 0.7 % and 1.0 % InPAG have been recorded by producing gels at each concentration and irradiating them to known doses with known D_max depths that could be investigated and measured from OCT. The 0.7 % samples were selected as the necessary concentration for a readily visible HU increase for planning purposes and was used to construct target region calibration samples. From a single batch of gel 5 samples were produced in 1 L PET containers. A cavity was set in these volumes that were then filled with InPAG and the containers flushed with N_2 gas to combat oxygen diffusion during gelation. The final samples were a 6cm depth of InPAG in the central axis of the container, surrounded by the same depth of nPAG, situating the expected depth of D_max in the centre of the field of view of the Vista OCT scanner.

2.2.2. Percentage Depth Dose. Using the method explained above two more samples without central InPAG volumes were produced, along with a full 1L PET jar. The partially filled gel containers were used to investigate the build-up region behaviour in the gels and confirm the depth of D_max. The fully filled container would then provide the data for the depth dose in the gel and have a full build-up region
and matched $D_{\text{max}}$ depth, which are usually obstructed by the sample holder and artefacts in the OCT reconstruction.

2.2.3. Irradiation of samples. All samples were placed in a water bath filled to a depth such that water surface was the same height as that of the gel. The surface of the gel was aligned at 100SSD and a machine output rate of 600 MU/min was used for all irradiations, from a Varian TrueBeam medical linear accelerator (linac) (Palo Alto, California). A 10x10 cm field of energy 6 MV was used for all irradiations overlaying the gel volume such that it fully contained the central InPAG volume. The target volume samples were irradiated to 0.8, 1.0, 1.2, 1.4 and 2.0 Gy, and the depth dose samples were irradiated to 1.2 Gy at $D_{\text{max}}$. All samples were then read out using a Modus Medical Devices (London, Ontario) VistaCT Optical CT scanner.

3. Results
The addition of Iodine contrast agent was expected to have an impact upon the chemical environment [6] and an impact upon the $Z_{\text{eff}}$ at imaging energies (~<140 kVp, ~50 kV mean energy), but a minimal physical interference for treatment energies of 6-10 MV. The changes to $Z_{\text{eff}}$ are illustrated in Figure 1.

![Figure 1. The effective atomic number of Water, DEFGEL(nPAG), and InPAG at energies from 0-20 MeV. The k-edge of Iodine is evident at 33 keV. $Z_{\text{eff}}$ calculations were performed using Auto-zeff software [6].](image)

3.1. Iodine Contrast Agent Concentration
The sharp increase in $Z_{\text{eff}}$ of the InPAG at 33 keV visible in Figure 1 is a primary reason why it is so valuable as medical imaging contrast material, the relationship between contrast agent concentration and HU is plotted in Figure 2. The various gel preparations were imaged inside a water bath in X-ray CT. The HU values are recorded as the mean of values along the central axis of the sample and off axis at three points throughout the height of the gel samples.
Figure 2. The mean increase in HU of a volume of nPAG containing Isovue as viewed in X-ray CT at 140 kVp. The variance of the signal is extremely low inside the dosimeter volume and as such produces very little uncertainty in the HU value. The error bars at each point are representative of the standard deviation in the HU within each sample.

From the curve displayed in Figure 2 it was determined that an Isovue concentration of 0.7% would provide a satisfactory contrast of InPAG(62 HU) surrounded by nPAG(16 HU).

3.2. Dose Response
The calibration points for the dose response curve of InPAG were taken from a region of interest in the slice that occurred at depth \(D_{\text{max}}\) for a 6MV beam, 1.6cm below the surface. The results of this analysis are plotted in Figure 3.

Figure 3: The change in optical density due to irradiation in a 6MV 10x10cm field at 100SSD for InPAG and nPAG in the same gel volume. The OD values are recorded for ROIs at \(D_{\text{max}}\). Uncertainty in the OD values is represented by the error bars present in this plot, being derived from the standard deviation in each of the ROIs examined. The larger variance in InPAG is likely due to tears caused by removing the test tube used to create a cavity.
The calibration curve plotted in Figure 3 was then used to calibrate the percentage depth dose curve that was extracted from the other containers. The PDD plotted in Figure 4 is a combination of 2 samples and the reasoning behind this approach is explained in the discussion.

![Figure 4](image-url)

**Figure 4.** Percentage depth dose as derived from 3 gel volumes delivered a nominal dose of 1.2 Gy at $D_{\text{max}}$, with OD values calibrated using the functions presented in figure 3 then normalised to the maximum dose value at $D_{\text{max}}$. The reference PDD in water from the machine used to irradiate the samples is included in red. The InPAG surface data points are hollowed to differentiate the two samples that the PDD curve data is taken from.

The surface region of the gel shallower than $D_{\text{max}}$ is likely to have its dose response inhibited to some degree by atmospheric oxygen. The flushing of the sample container with N₂ gas was intended to combat this problem and appears it has been only partially effective.

4. Discussion

The mechanism by which Iodine alters the dose response has not been clearly identified as of yet but it is proposed that it is a chemical change rather than a physical change in the amount of dose deposited. The Iodine is likely to change the consumption rate of one or both of the co-monomer units (Bis and Aam) used in nPAG. As the polymerization reaction is exothermic there is also a significant amount of pre-irradiation auto-polymerisation that can be caused by the addition of the Iodine. The dose response curve observed in Figure 3 is likely to be dominated by the reaction of a single monomer ingredient, inhibiting the dynamic range of a dosimeter containing Iodine.

As has been the case of all polymer gel dosimeters oxygen continues to be a problematic factor in production of reliable dosimeters [7-9]. The method of production used in this study included several steps at which oxygen permeating the gel matrix would cause problems. Even with the dosimeter containers being flushed with an inert gas (N₂) it is expected that some damping of dose response occurred at the gel surfaces that were exposed and as such reduced the observed signal. This is most impactful in Figure 4 when examining the buildup region and the apparent depth of $D_{\text{max}}$ at 16 mm. More investigation into what is a permissible pre-irradiation gelation time for limiting the extent of atmospheric oxygen diffusion is necessary for complete quantification of the PDD and calibration curves.
5. Conclusion
The addition of Isovue to nPAG is shown to increase the HU as expected, to a degree that makes it easily visible and contourable on X-ray CT for the purposes of treatment planning. The concentration of Isovue needed for this HU was asserted as 0.7 % w/w and the dosimetric impact of this quantity was investigated. The iodine is shown to alter the dose response curve compared to nPAG, with variances of the dose response noted. By careful combination of percentage depth dose curves from multiple samples a PDD of InPAG was produced, which has significant worth in understanding the dose response in the material when analyzing 3D dose distributions. The PDD exhibited some inhomogeneous dose response within the volume and the investigation of the causes of this will be the subject of further study [10-12].

6. References
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