MRI in Clinical Radiation Oncology: Dosimetry and Patient-Specific Plan Verification

Niko Papanikolaou, Ph.D.[1]; Geoffrey D. Clarke, Ph.D.[1]; Lora T. Watts, Ph.D.[1]; Thomas G. Maris, Ph.D.[2,4]; Evangelos Pappas, Ph.D.[3,4]

[1] University of Texas Health Science Center, San Antonio, Texas, USA
[2] University of Crete, Medical School, Heraklion, Crete, Greece
[3] Technological Educational Institute, Athens, Greece
[4] R&D department at RTsafe S.A., Athens, Greece

Introduction

The role of MRI in radiation oncology has been continuously evolving over the past decade. Radiation treatment planning, delivery and patient monitoring have been enriched through the increased use of MRI in radiotherapy clinical practice. Although MRI was originally introduced and continues to be a superb imaging modality for soft tissue characterization it has so far been used exclusively for imaging studies in humans and animals. There is however a novel application of MRI in the evaluation of radiation dose delivered to a phantom using dosimetry gels. Although the idea of gel-based dosimetry was introduced over two decades ago, its application in patient specific clones, with the explicit purpose of performing patient specific plan verification, is less than a year old.

Polymer gel MRI dosimetry was first introduced in 1993 and a large number of scientific publications exists on this topic, including a review by Baldock et al. [1]. The essence of this dosimetric method is that the local polymerization induced to a polymer gel after it has been irradiated, can be detected and quantified by MRI. The higher the dose absorbed within an elementary voxel of a polymer gel, the higher the amount of polymerization within that voxel and therefore the slower the water molecules motion within it, resulting in a lower T2 spin-spin relaxation time. Therefore, absorbed dose and T2 are directly and monotonically related. Accurate and quick measurements of T2 values can thus be converted to dose measurements. Moreover, given the 3D nature of MR scanning, polymer gel MRI dosimetry is inherently a 3D-dosimetry method.

Polymer gel MRI dosimetry has not entered radiotherapy clinical practice, mainly because of the practical issues of access to an MRI scanner, but more importantly because there was no demonstrable need for accurate 3D dosimetry in stylized phantoms. Consequently, polymer gel MRI dosimetry was until recently a research topic rather than a clinical tool. However, in early 2015 a novel application of gel dosimetry was introduced, whereby polymer gels were used as an end-to-end quality assurance and patient-specific plan verification process in radiotherapy [2-4]. An increasing number of radiotherapy centers world-wide have already started to adopt this novel clinical tool which has now been commercialized by RTsafe S.A. (Athens, Greece).

Gel dosimetry provides a new opportunity and a challenge for MRI scanners in the arena of clinical radiotherapy: how to obtain quick and accurate measurements of T2 relaxation times in three dimensions with minimal spatial distortions. We have found that the 2D HASTE multi echo Carr-Purcell-Meiboom-Gill (CPMG) sequence addresses this challenge.

The challenges with MRI T2 relaxometry in polymer gel dosimetry and the way by which the HASTE pulse sequence addresses these challenges are described below. A clinical example of the use of an MRI scanner with gel dosimetry for patient-specific dosimetric and geometric plan verification is also presented for a clinical case of a multiple metastases SRS treatment.

MRI HASTE T2 relaxometry in polymer gel dosimetry

In polymer gel MRI dosimetry, the R2 spin-spin relaxation rates (R2=1/T2) are linearly related with the absorbed radiation doses. This is the basic relationship present on the radiation induced polymerization phenomenon which shortens the T2 values which in turn, are measured by MRI techniques in polymer gel dosimetry. Their relationship (R2 vs. Dose) serves a linear calibration curve dependent on the chemical composition and the fabrication conditions of the gel material. A plethora of chemical formularies and fabrication procedures exist in the literature, all being suitable for gel dosimetry [1]. The purpose of this analysis is twofold. Firstly, to present the clinical MRI T2 relaxation measurement sequences available on all commercial Siemens MRI scanners that are used for the measurement of

the Vinylpyrrolidone (VPL) based polymer gel dosimeters [5-8], and secondly, to present the solution of the HASTE sequences for the T2 relaxation measurements in polymer gel dosimetry.

The basic rationale is that all of the T2 measurements can be performed by utilizing sequences that exist on all Siemens commercial clinical MRI systems. There are four distinct technical challenges.

Challenge 1: To accurately measure with MR imaging T2 values ranging from approximately 1000 ms to 200 ms, for pre and post irradiation respectively of a VPL polymer gel receiving a dose of 30 Gy.

Challenge 2: To obtain the best possible in-plane and cross-plane spatial resolution. An ideal resolution would be an MR image with a voxel size of 1 x 1 x 1 mm³.

Challenge 3: To achieve the best possible geometrical representation of true physical volumes throughout the total depicted imaging volume by eliminating any geometrical distortions.

Challenge 4: To limit the total examination time to a minimum while maximizing the measured signal-to-noise-ratio (SNR).

The quest is to produce an MRI sequence that satisfactorily addresses all four challenges.

Addressing challenge 1:

We need an accurate and fast multi-echo sequence designed for T2 relaxometry, covering a range of T2 measurements between 200 and 1000 ms. The existing MR sequences on a Siemens clinical MRI system are:

a. The 2D SE multi echo PHAPS sequence

This sequence is implemented on a 2D mode. Its advantages and disadvantages for multi-echo T2 relaxometry are:

Advantages: 32 equidistant echoes, use of high receiver bandwidths, same receiver bandwidth on each echo

Disadvantages: No 3D mode, no physical space filling on the 2D mode, no possibility of choosing asymmetric echoes in time, no use of RF restore pulses, long imaging time for either single or multi slice acquisition

b. The 2D TSE (RARE) multi echo CPMG sequence

This sequence is implemented on a 2D mode. Its advantages and disadvantages for multi-echo T2 relaxometry are:

Advantages: Physical space filling on the 2D mode, use of high receiver bandwidths, same receiver bandwidth on each echo, use of RF restore pulses, imaging time is reduced by increasing the Echo Train Length (ETL) factor and is independent from the chosen number of slices

Disadvantages: Only 3 echoes, no 3D mode, no possibility of choosing asymmetric echoes

c. The 2D HASTE multi echo CPMG sequence

This sequence is implemented on a 2D mode. Its advantages and disadvantages for multi-echo T2 relaxometry are:

Advantages: Physical space filling on the 2D mode, use of high bandwidths, same bandwidth on each echo, choice of asymmetric echoes, use of restore pulses, imaging time is only related to the number of slices. It is reduced by minimizing the number of slices and is kept minimum, due to the use of the highest possible ETL factor

Disadvantages: Only 4 echoes, no 3D mode

Addressing challenge 2:

The highest possible in-plane and cross-plane spatial resolution is required. Spatial resolution can be expressed by the MR image voxel physical dimensions and is mainly dependent on the gradient strength of the MR system. In-plane spatial resolution is fundamentally related to the physical dimensions of the selected field-of-view (FOV) and the raw data reconstruction matrix. Cross-plane spatial resolution (slice thickness) depends on the slice selection gradient strength. In cranial T2 relaxometry, where an FOV of 250-300 mm is used, an in-plane spatial resolution of 1 x 1 mm² and a cross-plane spatial resolution of 2 mm could be easily achieved. This spatial resolution of 1 x 1 x 2 mm³ is the practical limit, when using all of the above MR relaxometry sequences on most of the Siemens clinical MR systems. Spatial resolution can be improved by using software spatial interpolation to 0.5 x 0.5 x 1 mm³.

Addressing challenge 3:

Appropriately designed MR sequences and methods are needed to eliminate MRI geometrical distortions, related either to the system's hardware problems like gradient non-linearities or B_0 inhomogeneities, or to distortions induced by the scanned objects themselves. Geometric distortions related to systems' hardware problems can be eliminated either by extensive gradient calibration and Eddy current compensation procedures or by post-processing distortion correction software tools. Software distortion correction data can be obtained from the use of special MRI phantoms covering large imaging volumes.

Geometrical distortions of scanned objects can originate either by chemical shift spatial miss-registrations or by magnetic susceptibility artifacts which in turn distort the local magnetic field homogeneity. Fortunately, both types of such object-related geometric distortions can be eliminated by the use of the highest possible receiver bandwidths embedded on special MR sequences. Receiver bandwidths strongly depend on the MR systems' gradients. The higher the gradients used the higher the receiver's bandwidths.

In cranial T2 relaxometry, a typical receiver bandwidth of 500 Hz/pixel or greater is a prerequisite when using Siemens MRI systems with gradient strengths at the range of 30 mT/m. Such a high bandwidth is capable of eliminating to a large

extent most of scan object induced geometric distortions.

Addressing challenge 4:

Fast MR sequences are necessary to reduce examination time and maintain SNR to an acceptable practical level (SNR > 80, at a field strength of 1T, for a standard 2-channel Head CP coil). However, we also have to keep spatial resolution to the above-mentioned practical limit of 1 x 1 x 2 mm³. HASTE sequences are by definition the fastest MR sequences available on the Rapid Acquisition with Relaxation Enhancement (RARE) regime. They were developed specifically to minimize the patient scan time.

In cranial T2 relaxometry, HASTE sequences can be modified by utilizing a multi-echo pattern of 4 non time equidistant echoes for the goals of relaxometry. SNR is maintained to more than the practical acceptable level for a spatial resolution of 1 x 1 x 2 mm³. Therefore, HASTE sequences are the solution to challenge 4. For the Siemens clinical MR systems, equipped with the standard 8-channel phased array head coil, a standard cranial HASTE T2 relaxometry examination time is in the range of 10-15 minutes.

By summarizing all the above challenges and respective solutions we can confidently conclude that HASTE sequences address all four challenges and as such are ideal for the T2 relaxometry methods applied for MRI gel dosimetry. Polymer gels suitable for MRI gel dosimetry purposes have T2 relaxation times that practically mimic soft tissues and human body fluids. HASTE sequences were designed to image soft tissues and human body fluids in the shortest possible examination times. Clinical HASTE sequences can therefore be easily modified by incorporating multi-echo trains in order to measure T2 relaxation times of dosimetric gel materials. In our implementation, we are using 4 echoes in a single echo train for T2 value measurements.

HASTE sequences can accommodate an RF restore pulse in order to restore longitudinal magnetization back to its equilibrium state prior to the following excitation. This technique is of paramount importance because it allows the users to keep TR (repetition time) as low as 2000 ms while accurately measuring T2 values. This feature has an important effect on the reduction of imaging time. Moreover, the possibility of using non-equidistant echoes is also one of the great advantages of the HASTE sequences, because it increases T2 measurement sensitivities for the chosen measurement range of T2 values in MRI gel dosimetry.

The last but not least advantage of the HASTE sequences is their time dependence on the number of anatomical slices. The fewer the slices obtained, the less the acquisition time. HASTE sequences are designed to operate in a sequential rather than an interleaved way. This means that each slice is acquired in one TR. This is not the case in all the other relaxometric sequences where parts of each slice are obtained in each TR. Acquisition time is linearly related to the TR factor. The main advantage therefore is that we can have a predefined set of slices covering a specific irradiated volume or multiple volumes, without having to cover the entire brain anatomy for the scan. This feature can dramatically reduce imaging time to the order of seconds, while maintaining high sensitivity for measuring T2 values.

Clinical example: Patient-specific pre-treatment plan verification of a single isocenter multiple-metastases SRS treatment

A single-isocenter 6-metastases SRS treatment plan has been implemented for a selected patient (details regarding the software and hardware used for the implementation of the treatment plan and the SRS treatment itself are out of the scope of this brief clinical example). The patient planning CT scans were used for the production of a 3D-replica of the selected patient that was printed with sub-millimeter accuracy (Fig. 1). This 3D-printed replica was then filled with a VPL polymer gel. The final product was a patient-specific dosimetry phantom that was used for patient-specific plan verification (this service is commercially available and marketed by RTsafe S.A.). This patient-specific phantom was then irradiated as if it was the actual patient, i.e. set-up, image guidance and irradiation were applied to this patient-specific phantom as would have been done to the real patient (the 3D printed bone structures of the phantom simulate accurately the real patient bones in terms of its interaction with radiation. Moreover, the polymer gel that fills the phantom simulates soft tissue in terms of its interaction with radiation). A 2D HASTE multi echo CPMG sequence was used for MRI scanning of the irradiated phantom.

This patient-specific dosimetry phantom was scanned on a 3T superconducting MR imager (MAGNETOM Trio, A Tim System, Siemens Healthcare, Erlangen, Germany. Gradient strength: 45 mT/m, slew rate: 200 mT/m/s). A standard quadrature RF body coil was used with all measurements and a standard 8-channel phased array head coil was used for signal detection. The phantom was placed in the supine position and entered the magnet cradle using the head-first configuration, by exactly mimicking the real patient positioning for a standard MRI head examination. A conventional gradient echo (GRE) 2D multi slice multi plane turbo Fast Low Angle Shot (turboFLASH) T1-weighted imaging sequence was initially applied in axial, sagittal and coronal planes for the localization of the phantom head anatomy.

Once localized, a series of a 2D, multi slice, multi echo, Half fourier Single Shot Turbo Spin Echo (HASTE) PD to T2-weighted sequence was utilized sequentially with no interslice delay time. The HASTE sequence was applied using 4 asymmetric spin echoes. The first TE was 36 ms and the rest 3 TEs were obtained thereafter approximately every 400 ms. With the above chosen parameters a sensitive multi-echo sequence for T2 measurements ranging from 1000 ms down to 200 ms was obtained. The relative HASTE sequence contrast related

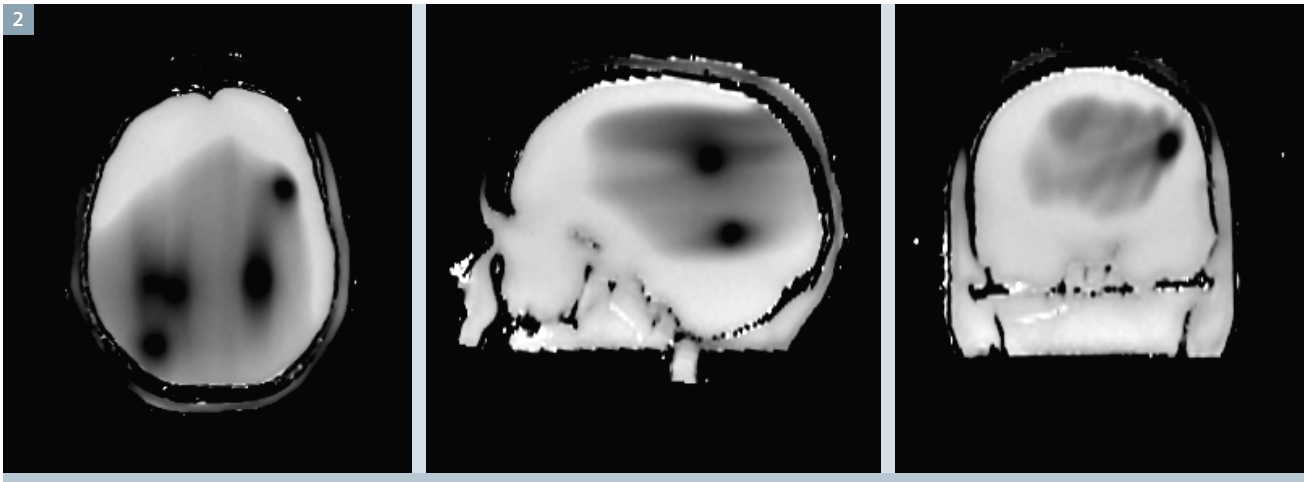
1 Photographs of the 3D-printed patient-specific phantom just before its filling with VPL based polymer gel.

parameters were therefore: (TR/TE1/TE2/TE3/TE4/FA: infinite/36 ms/436 ms/835 ms/1230 ms/90°). An effective TR of 2000 ms was used. A standard RF restore pulse was used prior to next excitation in order to minimize examination time.

77 contiguous space filling oblique axial slices of 2 mm slice thickness were used. A FOV image area of 350 x 219 mm² was covered from each slice. The image reconstruction matrix was 256 x 160 pixels respectively to the FOV dimensions, corresponding to a square pixel matrix with pixel dimensions 1.4 X 1.4 mm² (in-plane spatial resolution). The cross-plane spatial resolution was equal to the slice thickness (2 mm). The overall spatial resolution expressed in raw data voxel dimension was 1.4 x 1.4 x 2 mm³. The total space filling imaging dimension on the cross-plane direction was 154 mm, covering the entire cranial anatomy.

The longer anatomical axis (anterior to posterior direction for the axial oblique slices) was chosen each time as the frequency encoding axis. The highest possible receiver bandwidth (781 Hz/pixel) was used in order to eliminate geometric distortions due to susceptibility artifacts. Geometric distortion filtering was also applied in order to eliminate geometric distortions due to inherent gradient field imperfections. The ETL factor for the specific HASTE sequence was 160 and the echo spacing was 4.54 ms. The overall SNR measured on the first echo proton density image was 280. 14 signal averages were used and the total examination time was approximately 20 minutes.

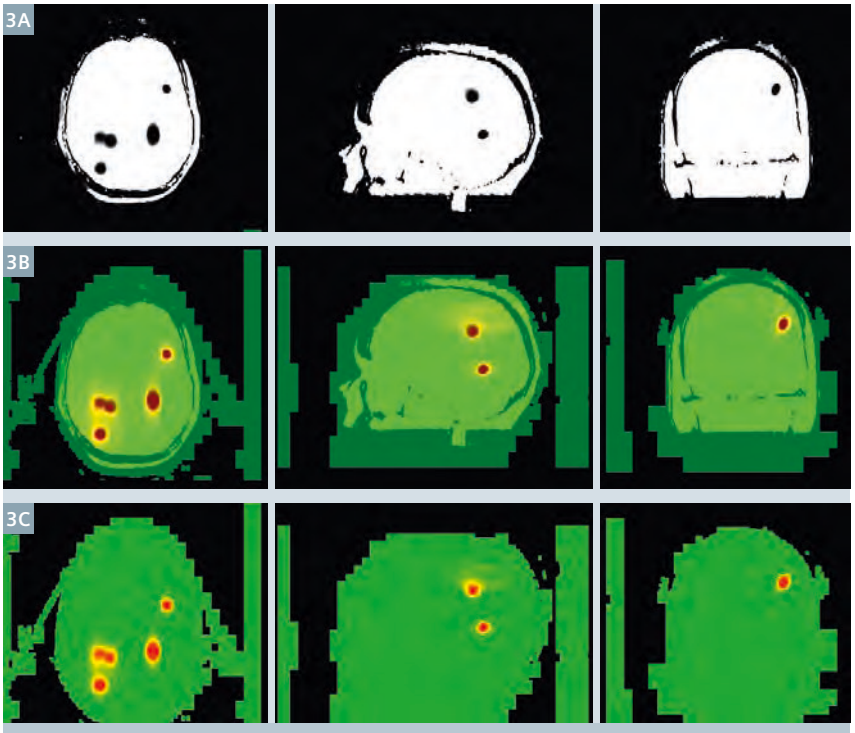
T2 measurements were obtained by utilizing the T2 HASTE quantitative MRI (T2-HASTE-QMRI) multi slice protocol, applied in reference to all 77 space filling slices. As a final result 77 space filling T2 calculated parametric maps were obtained, which were consequently transformed to 77 space filling relative dose maps. The minimum sensitive dosimetric volume was determined simply by the raw data voxel dimensions and was 1.4 x 1.4 x 2 mm³.



2 MRI T2 maps of the irradiated patient-specific phantom, derived using the 2D HASTE pulse sequence. Dark areas are the **low** T2 and therefore **high dose** areas. Brightness and contrast are adjusted so that high and low dose areas are depicted.

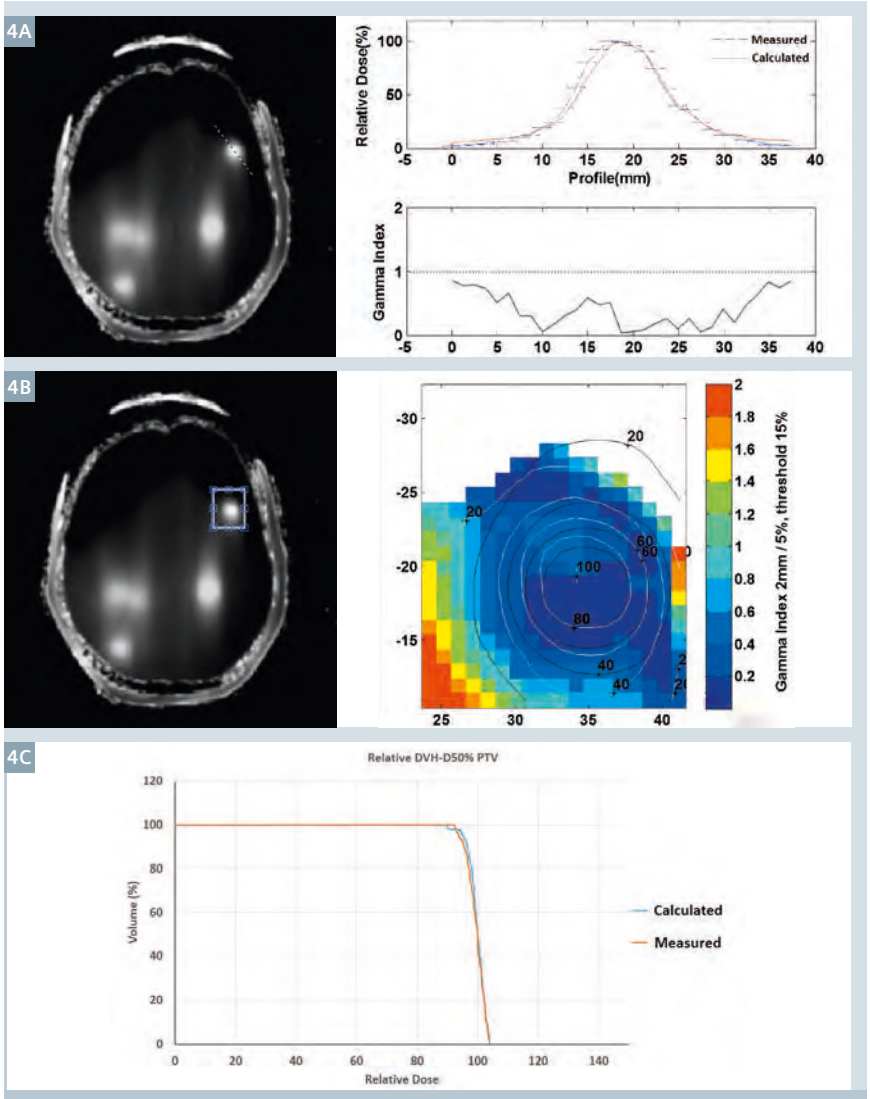
The MRI scans were used for the calculation of 3D-T2 maps. These T2 maps include the 3D dose information. The dark areas (low T2) are the high dose areas (Fig. 2) and the dose to (1/T2) linear relationship was measured using a calibration process.

The 3D-printing sub-millimeter accuracy of the patient-specific dosimetry phantom, allows a co-registration between the real patient planning CT scans (that also include the RTstructures and RTdose data in the same reference space) with the T2 maps of the irradiated phantom (Fig. 3). A first qualitative analysis reveals that the delivered dose (MRI scans) satisfactorily matches with the calculated dose (Treatment Planning System (TPS) RTdose data). The T2 maps correlate to the full 3D dose of the treatment that has been delivered. From the dose to (1/T2) calibration curve, the 3D T2 map was converted to a 3D dose map. Comparisons between the TPS RTdose calculations and the experimental 3D dose data are now possible. Therefore, quantitative data can be derived (Fig. 4).



3 MRI T2 maps of the irradiated patient-specific phantom depicting the **actually** delivered dose, blended with 'RTdose' corresponding TPS **calculated** dose. **(3A)** MRI 100% – TPS 0%, **(3B)** MRI 50% – TPS 50%, **(3C)** MRI 0% – TPS 100%. Brightness and contrast adjusted so that only high dose areas are depicted. The T2 maps are co-registered to the real patient planning-CT scans. Therefore, a direct qualitative comparison with the TPS derived 'RTdose' data is feasible. A first qualitative inspection shows a satisfying spatial accuracy of dose delivery.

A significant number of radiotherapy centers, including University of Texas Health Science Center (San Antonio, TX, USA), The Royal Marsden NHS Foundation Trust (London, UK), the Institut Sainte Catherine (Avignon, France), Ichilov and Assuta Medical Centers (Tel Aviv, Israel) and the University of Freiburg (Freiburg, Germany) have started to implement end-to-end quality assurance tests and/or patient-specific plan verification procedures using this novel technique and their Siemens MRI scanners. Conclusively, a significant amount of data exists that supports the use of gel dosimetry for patient treatment QA and the claim that the HASTE pulse sequence is ideally suited to perform such 3D dosimetry measurements.



4 Quantitative dosimetric information derived by MRI T2 relaxometry performed using 2D HASTE pulse sequence. **(4A)** 1-D dose profile comparison. MRI measured dose profile vs. TPS calculated dose profile. 1-D gamma index (2 mm DTA / 5% dose difference). The profile corresponds to the line superimposed on the MRI-derived dose measurements depicted in the image on the left. **(4B)** 2D gamma index map and relative isodose lines comparison between the measured (MRI derived) and calculated (TPS derived) doses. The area where the 2D gamma index was calculated is superimposed on the MRI-derived dose measurements depicted in the image on the left. **(4C)** Dose Volume Histogram (DVH) inter-comparison for one of the six metastasis treated. MRI-derived measured DVH versus TPS-derived calculated corresponding DVH.

References

1 Baldock C, De Deene Y, Doran S, et al. 'Polymer gel dosimetry', Phys Med Biol. 2010, Mar 7;55(5):R1-63.

2 Papanikolaou N., Pappas E., Maris T.G., Teboh Forbang R., Stojadinovic S., Stathakis S., Gutierrez A.N. 'Stereotactic Treatment of Multiple Brain Metastasis: Pseudo In Vivo Evaluation of Three Different Techniques', International Journal of Radiation Oncology * Biology * Physics, 2015,93(3):E572.

3 Pappas E., Maris T.G. , Kalaitzakis G., Boursianis T., Makris D., Maravelakis E. 'Innovative QA methodology for true patient-specific Dose Volume Histograms (DVHs) measurements', Radiotherapy and Oncology, 2015, Vol.115, S704-S705.

4 Pappas E., Maris T.G., et al. "An innovative method for patient-specific pre-treatment plan-verification (PTPV) in head & neck radiotherapy treatments: preliminary results" International Journal of Radiation Oncology * Biology * Physics 2013, Vol. 87, Issue 2, Supplement, Page S756-7.

5 Papoutsaki MV, Maris TG, Pappas E, et al. "Dosimetric characteristics of a new polymer gel and their dependence on post-preparation and post-irradiation time: Effect on X-ray beam profile measurements. Phys Med. 2013, S1120-1797(13).

6 Pappas E., Maris T.G., Manolopoulos S., Zacharopoulou F., et al. "Small SRS photon field profile dosimetry performed using a PinPoint air ion chamber, a diamond detector, a novel silicon-diode array (DOSI) and polymer gel dosimetry. Analysis and intercomparison" Med. Phys. 2008, 35(10), p.4640-4648.

7 Papadakis A.E., Maris T.G., Zacharopoulou F., Pappas E. et al. An evaluation of the dosimetric performance characteristics of N-vinylpyrrolidone-based polymer gels. Phys. Med. Biol. 2007, 52, p.5069-5083.

8 Pappas E., Maris T.G., Papadakis A., et al. Experimental determination of the effect of detector size on profile measurements in narrow photon beams. Med. Phys. 2005, 33(10), p.3700-3710.

Contact

Niko Papanikolaou, Ph.D.
University of Texas
Health Science Center
7703 Floyd Curl Dr
San Antonio, TX 78229
USA
Phone: +1 (210) 450-5664
papanikolaou@uthscsa.edu

Contact

Evangelos Pappas, Ph.D.
TEI
RTsafe, www.rt-safe.com
48 Artotinis Str.
116 33 Athens
Greece
Phone: +30 2107563691
epappas@rt-safe.com