

Monomer consumption in MAGIC-type polymer gels in the Bragg-peak of proton beams observed by volume selective ^1H MR-spectroscopy (MRS): proof of principle for high resolution MRS-methodology with a sensitive rf-detector

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Abstract. Mono-energetic proton and heavy ion beams for tumour therapy feature high dose gradients laterally and at its penetration depth, characterized by the Bragg-peak. The 3-dimensional dosimetry of such Hadron particle beams poses high demands on the spatial resolution of the imaging methodology and linearity of the polymer gel dose response in a wide dose range and at high linear energy transfer (LET). In almost all polymer gels the Bragg-peak dose response is therefore quenched. Volume selective MR-spectroscopy is in principle capable of delivering information on the polymerization process. We here present the MR-methodology to obtain MR-spectroscopic (MRS) data on the monomer consumption at the very small voxel volumes necessary for resolving e.g. the Bragg-peak area. Using additional hardware components, i.e. a strong gradient system and a very sensitive rf-detector at a high field human 7T scanner, MR-microimaging and MRS with 600 μm depth resolution can be implemented at very short measurement time. The vinyl groups of methacrylic acid in a MAGIC-type polymer gel can be resolved by volume selective MRS. The complete monomer consumption in the Bragg-peak due to polymerization is demonstrated selectively in the Bragg-peak indicating one main reason for Bragg-peak quenching in the investigated polymer gel.

1. Purpose/Introduction

The 3D-dosimetry of proton ion beams for tumor therapy with single energy remains difficult due to the fine dose placement in the Bragg-peak. For evaluation beyond planar film dosimetry 3D-arrangements of pin-point ionization-chambers are used as standard for the verification of treatment planning systems [1]. However the spatial resolutions (voxel volume) determined by the ionization chamber distances in these arrangements are significantly lower (10^3) than achievable with polymer gel dosimetric imaging [2, 3]. The MR-Parameter T2 has shown to be most sensitive to the polymerization process in polymer gels subsequent to irradiation [4, 2]. T2-maps can be obtained for



resolving the Bragg-peak region [5-8]. Besides from other factors, the spatial resolution in imaging is critical for the accurate determination of dose in the fine Bragg-peak enhancement area for single particle energy [7]. T2-parameter imaging does not give detailed insight in the molecules involved during the polymerization procedure and the amount of monomer consumption. FT-Raman spectroscopy has been applied for the analysis of monomer consumption in acrylamide-Bis-acrylamide polymer gel variants [2]. It has also been demonstrated, that Magnetic Resonance (MR)-spectroscopy and spectroscopic imaging might yield useful information on the relative consumption in the monomer co-monomer mixture in a photon field for poly-acrylamide and methacrylate-co-monomer gels [9]. MR-spectroscopic imaging using a chemical shift selective refocusing pulse might even be used in principle for dosimetric imaging [9].

Heavy ion and proton therapy is characterized by the high ionization density along and especially at the very end of the beam path, i.e. high linear energy transfer dE/dz in the Bragg-peak regime [6] (see figure 1). In addition the high deposited energy per unit mass might result in a complete consumption of the monomer in the very small volume characterized by the Bragg-peak and thus quenching of the dose response in T2-imaging in this region ("Bragg-peak quenching").

Volume selective MR-spectroscopy (MRS), adapted to the very small volumes in the Bragg-peak, might be capable of the detection of this monomer consumption. We therefore investigated, whether it is possible to measure the monomer concentration at the very small voxel volumes within and outside of the Bragg-peak area, using a high field (7T) human MR-scanner equipped with a microscopy insert with a highly sensitive rf-detector.

2. Materials and methods

2.1. Polymer gels

We have manufactured several sets of "normoxic" polymer gels with different additives for sensitivity and dose range modifications. The presented data belongs to a variant using ascorbic acid and copper-sulfate (similar to MAGIC gels [10]) as oxygen scavenger, methacrylic acid MAA (6% w/w) as monomer, gelatin (14% w/w) and water. The MAGIC-variant exhibited a linear dose response in the investigated dose range up to the maximum dose $D_{\max} = 48$ Gy (figure1). The polymer gel is filled into Barex[®] flacons (o.d = 28 mm) to avoid oxygen penetration from outside. The polymer gels were irradiated with a mono-energetic proton ion beam.

2.2. Irradiation

For reference ⁶⁰Co-photons were applied to the same type of polymer gels. The T2-response for the polymer gel variant was measured. The specimen at $D = 0$ and $D = 16$ Gy were also investigated by MRS. Mono-energetic ($E = 59.8$ MeV) proton beams for human therapy were applied to the polymer gel at a beam diameter of 6cm at the Heidelberger Ion-beam-Therapy-center (HIT). The penetration depth for this beam amounts to about 28 mm in water. The investigated sample experienced a dose of $D = 32$ Gy (plateau).

2.3. Magnetic resonance imaging and spectroscopy

Hardware: The high spatial selectivity with small voxels in MRS was achieved on a 7T human ultra-high-field MR-scanner, equipped with a small sized (i.d. 90 mm) strong gradient system ($G = 750$ mT/m) [11]. A very sensitive solenoid type detector (i.d. 28.5 mm) was designed particularly for the use with the Barex[®] flacons. Numerical simulations were performed to optimize the geometry of the solenoidal radiofrequency (rf-) detector to improve the homogeneity within the sample volume [12]. A customized housing was designed and built to fit the detector into the gradient insert and allow frequency adjustment and impedance matching from the outside.

Pulse-sequence and protocols: T2-weighted images using Multi-slice multi echo imaging are obtained for reference position (Fig.3a). FOV= (70 mm)², voxel size = (0.546)² x 1 mm³, Matrix = 128 x 128, TE = 10 ms; 20 echoes. MRS-data was obtained within 2 min at a voxel size of 12 x 12 x 0.6 =

8.6 mm³ with a depth of 600 μm in the beam direction, necessary to spatially resolve the Bragg-peak area. Volume selection was achieved with a STEAM pulse sequence [13] (TR = 6 s, TE = 15 ms, av:16, TM < 100 s). The samples were shimmed manually to a water line-width of about 20-40 Hz.

3. Results

The polymer gel variant exhibits a linear dose response to ⁶⁰Co-photons up to the maximum investigated dose level D_{max} = 48 Gy (figure 1). A high-resolution proton ion beam dose-map of the polymer gel, irradiated with D = 32 Gy (plateau), is shown in figure 2a. The sharp dose edge at the Bragg-peak is clearly delineated.

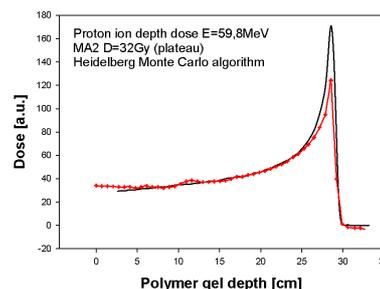
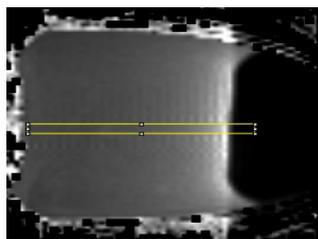
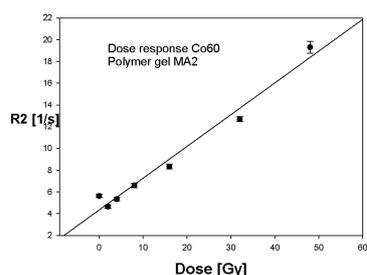
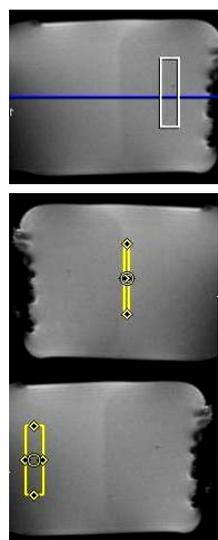


Figure 1: Relaxation rate ($R2 = 1/T2$) of the polymer gel MA2 to the dose (⁶⁰Co-photons). The dose response is linear in the investigated range from D = 0 up to 48 Gy.

Figure 2a: Dose image calculated from a T2-map of the polymer gel irradiated with a proton beam at D = 32 Gy (plateau). The beam enters at left and penetrates the polymer gel until absorption at the Bragg-peak (bright line at right).

Figure 2b: Dose profile along the indicated path in figure 2a. For reference the result of a Monte-Carlo-simulation for the depth dose path is indicated (normalized to 32 Gy in the plateau and shifted to Bragg-peak coincidence).

Volume selective ¹H-spectroscopic data is shown for three different regions of interest in figure 3:



top: position behind the Bragg-peak in area of no dose and no polymerization,

center: small sized volume in the Bragg-peak,

bottom: position of the MRS selected volume in the plateau.

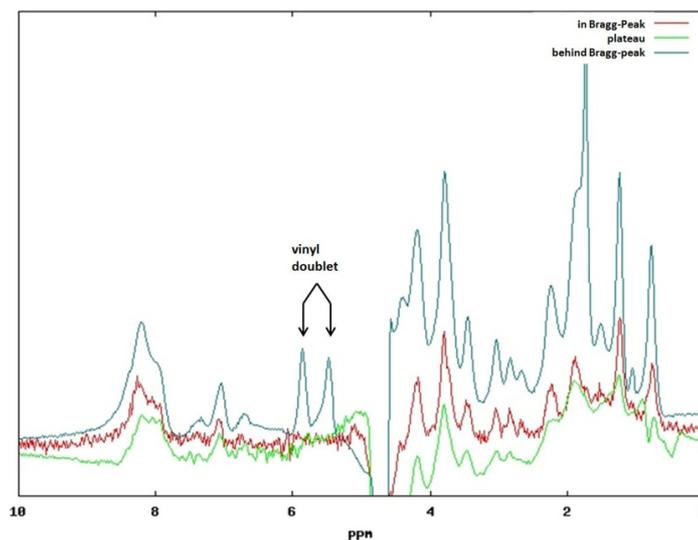


Figure 3a: Positions of the detected volume for ¹H -volume selective MR-spectroscopy.

Figure 3b: ¹H-MR-spectra from volumes as indicated in figure 3a. Behind the Bragg-peak at D=0Gy the doublet signal of the vinyl protons at 5.4 and 5.8 ppm (arrows) from the monomer is clearly observed. The vinyl doublet disappears in the Bragg-peak (medium spectrum, red) indicative of the monomer consumption.

1. Behind the Bragg-peak (figure 3a, top), i.e. in a region of presumably no dose. The topmost (grey) spectrum in figure 3b reveals the vinyl doublet signal (s = 5.4 and s = 5.8 ppm), connected to the

protons near the double bindings of the carbon atoms in MAA. For $D=0$ Gy, the doublet-signal is enhanced, indicating high concentration of 6% for MAA in the investigated polymer gel.

2. In the *plateau region* (figure 3a, bottom), the vinyl group doublet is already strongly reduced, indicating monomer consumption (figure 3b, light green spectrum).

3. In the small detected volume *in the Bragg-Peak* (figure 3a, center), the vinyl group has completely disappeared (figure 3b, medium spectrum, dark-red line), indicating that the monomer is completely consumed and the dose response might be suppressed in the Bragg-peak.

4. Discussion/Conclusion

Using additional hardware components, i.e. a strong gradient system and a very sensitive object adapted rf-detector in combination with an ultra-high field human 7 T scanner, volume selective spectroscopy can be implemented even at the very small voxel volumes necessary for investigations of the Bragg-peak. In the MR spectrum, the doublet from protons near the vinyl double bond can easily be detected within 2 min measurement time. The reduction of monomer concentration due to polymerization can be observed. MAGIC polymer gels with a linear dose response far beyond (i.e. $D = 48$ Gy) a nominal entrance dose ($D_{\text{plateau}} = 32$ Gy) might exhibit significant dose quenching in the Bragg-peak due to complete monomer consumption. Molecule specific information, even in the Bragg-peak in a small area of high LET, as well as highly localized chemical information on the polymerization process in gel dosimetry can be obtained from volume selective spectroscopy. The absolute accuracy and stability of the spectroscopic polymer gel dose response, particularly in the Bragg-peak regime, still has to be investigated for different dose levels. Our findings might represent the basis for future calibration and quantification of spectroscopic data with regard to dose imaging based on MR spectroscopic imaging [9] at very high spatial resolution.

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