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Comparison of low dose proton and photon irradiation induced polymerization processes in advanced nMAG gels using Raman spectroscopy

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Abstract. A rapid development of the new radiation based cancer treatment technologies that are more individualized and patient oriented request precise 3D treatment dose verification methods in high dose gradient fields. Polymeric dose gels are excellent 3D dosimeters that allow analysis of spatial dose distribution in the irradiated target and also in the regions out of the target since the investigation of low dose induced secondary effects (secondary cancer, inflammations) stands on the priority list. Since the sensitivity of dose gel to different types of irradiation depends on radiation induced polymerization processes, in this work we present Raman analysis results related to advanced nMAG dose gels polymerization upon its irradiation with high energy photons and protons to doses ≤ 5 Gy.

1. Introduction

A growing up variety of different radiation based cancer treatment methods accelerates the development of the new dosimetry methods, new detectors for dose assessment and materials for these dosimeters. Well-known methods and dose registration devices (dosimeters) are also applicable if their characteristics meet the new requirements. It is known [1-3] that being nearly tissue equivalent polymer gel dosimeters can provide precise and high-resolution verification of complex 3D dose distributions in clinical radiotherapy, if adjusted to the type of radiation. A number of formulations of the radiation sensitive polymer gels that might be used as 3D dosimeters have been proposed indicating high potential for dose gel applications for 3D dosimetry in photon radiotherapy and are still being explored [4]. However it is evident that in special cases particle therapies (protons, light ions, neutrons) are more effective for cancer treatment. Proton therapy is becoming increasingly useful as an external beam radiotherapy modality because of its characteristic dose distribution. Taking into account that neutral photons interact with matter in different way as the protons do, at least in the sense of different LET (linear energy transfer effect), a question arises whether well-known dose gels [5] are sensitive enough to provide information on proton induced 3D dose distribution in these materials. Direct response to proton beam LET in novel polymer gel dosimeters has been already reported [6] however the problem of dose gel sensitivity to proton irradiation remained. In this frame investigation of proton induced polymerization processes in dose gels is of great importance. The usual dose response analysis in irradiated gel dosimeters is performed using certain modalities including MRI, X-ray computed tomography, optical CT, ultrasound. Raman spectroscopy might be also used for the evaluation of dose response in polymeric gels, but this technique is more dedicated and has high potential for the analysis of radiation induced changes in polymerized gel structures [2, 3]. The polymerization sensitivity of the



irradiated gel can be calculated from the intensity of the characteristic Raman bonds. This parameter provides irradiation dose related information on the efficiency of monomer consumption and polymer formation within the gel. Polymerization sensitivity for photon irradiated acrylamide or methacrylic acid based gels have been reported in [7, 8], however in the case of proton irradiation the most research is focused on the investigation of dose - LET dependencies in irradiated polymer gels and evaluation of the other irradiation parameters (RBE) [6, 9, 10].

Despite the availability of a certain amount of the data related to proton irradiated polymer gels, low dose (up to 10 Gy) induced changes in the formed polymeric structures are not investigated in details yet. Also the assessment of the dosimeter's suitability for low dose evaluation requires more targeted research of proton induced polymerization processes in gels, since fractionation and proton doses per fraction are different as compared to standard 2 Gy dose per fraction in photon radiotherapy.

The aim of this work was to compare photon and proton beam induced polymerization process in Methacrylic acid based advanced normoxic dose gels (nMAG) using Raman spectroscopy and assess their feasibility to serve as a 3D dosimeters also for the evaluation of low dose distributions in the "out of the target" regions irradiated during treatment of cancer patients. Raman spectroscopy has been chosen for the analysis since it is non-invasive method, is not affected by the presence of water in evaluated samples and therefore is advantageous when analyzing soluble and/or biochemical substances.

2. Materials and methods

2.1. Dose gel fabrication

Using UV-VIS spectrometry nMAG gels containing of 8% w/w of Methacrylic acid (MMA, 99%, Sigma-Aldrich); 2 mM of (hydroxymethyl) phosphonium chloride (THPC, Sigma-Aldrich); 6% w/w of gelatin (300 Bloom Type A, Sigma-Aldrich) and 86% of pure water were identified as being most sensitive to photon irradiation. Due to this, gels of the same composition were prepared for the investigation of photon and proton irradiation induced polymerization processes following usual gel fabrication procedure. Prepared gels were poured into PMMA standard disposable cuvettes (BRAND®, 45mm x 12.5mm x 12.5mm), left to settle for a 5 min and then tightly closed and left for 24 hours in dark and cool place.

2.2. Irradiation of gels

2.2.1. Proton irradiation of gels. Experimental samples of nMAG dose gels were irradiated in proton accelerator IBA PROTEOS C230 to 230 MeV at OncoRay Clinic in Dresden/Germany. Proton irradiation geometry was realized keeping gantry and treatment table orientations at 0° position. Farmer chamber PTW30013 with build-up cap was fixed in a central position of the irradiation field, which was formed applying 15.0 cm snout. This ionization chamber was used for the independent registration of proton irradiation dose which was assessed using electrometer UNIDOS E (PTW). Dose correction factor $k_0=1.022$ was calculated for this chamber taking into account atmospheric conditions: $p=1002.1$ hPa and $T=23.1^\circ\text{C}$. In each irradiation experiment two couples of cuvettes belonging to different batches with the same type of gel were positioned on the treatment table parallel to the ionization chamber on both sides of it. Arranged cuvettes were surrounded by 1.50 cm thick PMMA blocks and covered by the additional 10.3 cm thick PMMA block (corresponds to the thickness of 11.19 cm in water) in order to secure 10.0 cm width of modulated SOBP with a total proton beam penetration depth of 17.0 cm. Gel samples were irradiated to doses from the interval 0.5 - 5.0 Gy.

2.2.2. Photon irradiation of gels. The irradiation of gel samples with photons was performed in medical linear accelerator Clinac DMX (Varian) at Oncology hospital of Lithuanian University of Health Sciences. Following irradiation parameters were used: max dose depth was 1.5 cm, source to surface distance was set to 100 cm, field size 10×10 cm², dose rate - 3 Gy/min. 1 monitor unit (MU) of the Linac

corresponded to 0.01 Gy on average, however using calibrated ionization chamber the value of MU in terms of Gy was adjusted for each treatment procedure separately [11].

2.3. Evaluation of gels by Raman spectroscopy

In contrast to small - molecule compounds, in polymer molecules the atoms are linked together to form longer chains. The presence of such long chains causes additional vibrational modes of the whole chain that might be assessed using FT- Raman spectroscopy. It is well-known [12], that Raman spectroscopy is more sensitive to highly polarizable C-C and C=C groups, transformation of which during irradiation of gels play the most important role in gel polymerization process. FT- Raman scattering spectrometer (RENISHAW in Via Raman microscope) equipped with DPSS laser ($\lambda=532$ nm) was used for gel evaluation. Stokes line measurements were performed within the range of 250 cm^{-1} and 3600 cm^{-1} , resolution of measurements was better than 1 cm^{-1} . Silicon wafer was used to calibrate the Raman spectrometer for both Raman wavenumber and spectral intensity.

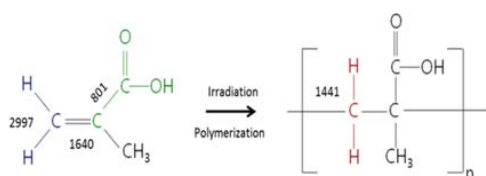


Figure 1. Basic polymerization process in MAG dose gels (adapted from [6]).

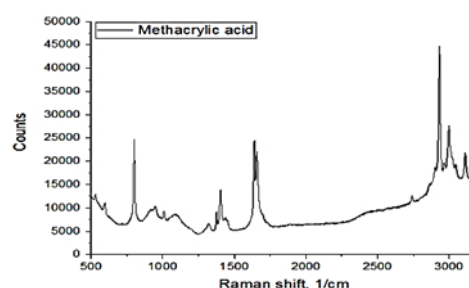


Figure 2. Raman spectrum of pure MAA (used for preparation of dose gels) with corresponding peaks: 801 cm^{-1} - ν (C-COOH), 1403 cm^{-1} - δ (CH_2), 1441 cm^{-1} - ν (CO)_s, 1640 cm^{-1} - ν (C=C), 2937 cm^{-1} and 2997 cm^{-1} - ν (CH_2)_s.

Irradiated nMAG gels were analysed 2 days after the irradiation. This time was needed for transportation of gel samples to host institution (OncoRay Clinic, Dresden, Germany) for proton irradiation and back, and was sufficient enough to complete photon or proton radiation induced polymerization process within the gel samples. Since nMAG gel does not contain any cross linker, two monomers of methacrylic acid (MAA) are interacting to start polymerization and precipitation of polymethacrylic acid (PMAA) upon irradiation (figure 1) thus forming small insoluble polymeric structures embedded in gelatine matrix. In order to follow polymerization process, characteristic frequencies (Raman peaks) of gel constituents before irradiation were evaluated analysing Raman spectra (figure2) or using information provided by other researchers [13, 14].

3. Results and discussion

It is known that carbon covalent bonds are tending to break into carbon single bonds upon irradiation (figure 1). Due to this the number of carbon single bonds increases, while the number of covalent carbon bonds decreases with the increasing radiation dose, indicating ongoing polymerization process. Analysis of dose dependent Raman peak intensity changes allows for the estimation of dose gel sensitivity parameters. It should be noted, that in order to enhance the sensitivity of experimental dose gels relative high amount of MAA (8%) was added to gel and the amount of gelatin was reduced to 6%. It was done taking into account that irradiated to higher doses gelatin starts interacting with methacrylic acid and forms polymer derivatives complicating the evaluation of dose gels. Also the polymerization level of dose gel is reduced due to additional consumption of methacrylic acid monomers in reactions with gelatin [15].

Raman spectra of the advanced nMAG dose gels after their irradiation to photon and proton beams are provided in figure 3 and figure 4 respectively.

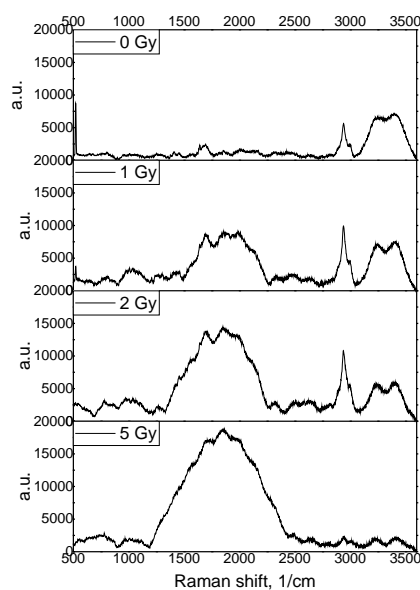


Figure 3. Raman spectra of photon irradiated nMAG gels

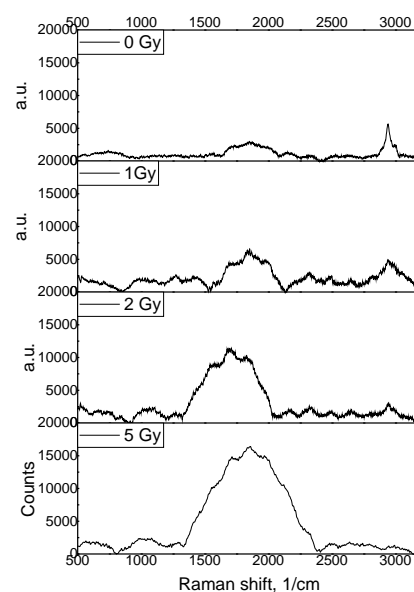


Figure 4. Raman spectra of proton irradiated nMAG gels

It was found that the most important Raman peaks of irradiated gels were slightly shifted towards higher Raman wavelength values and their exact positions were slightly altering with the dose. The overall shape and Raman spectrum development tendencies after gel irradiation were similar for both: photon and proton irradiated gels. A broad band seen in spectra between 1200 cm^{-1} and 2500 cm^{-1} was attributed to gelatin and imparted structures; another one seen between 3100 cm^{-1} and 3500 cm^{-1} was related to O-H vibrational modes in water. Growing Raman intensity with increasing irradiation dose indicated growing level of polymerization in irradiated gel. The broadening of the “gelatin” band indicated rearrangements in the gel structure and growing amount of formed polymerized derivatives embedded in the gelatin matrix. The increase of “gelatin” band intensity and its broadening was less expressed for gels irradiated to different proton doses, thus indicating lower sensitivity of gels to proton irradiation. It was explained by the fact that the decreased sensitivity of polymer gels may be attributed to a larger density of created polymer radical chains close to the proton tracks that favors a faster termination of the polymerization reactions. Occurrence of a sharp high intensity peak observed in initial gels around 2940 cm^{-1} was related to relative high amount (8%) of MAA, which was added to gel in order to increase its overall sensitivity. The difference in Raman spectra (at 0 Gy) for reference samples thought for proton and photon irradiation was caused by the fact that all (incl. reference) to proton irradiation facility transported samples underwent additional X-ray exposure during inspections at the airport. Raman spectrum of the transported reference samples was later on used for the evaluation of radiation induced changes in proton irradiated gel samples.

3.1. Evaluation of photon irradiated nMAG gels using Raman spectroscopy

Relatively well pronounced Raman peak at 809 cm^{-1} observed in all photon irradiated nMAG gel samples (figure 3) records symmetric stretching mode of C-COOH representing a bond between carboxylic carbon and double bond carbon. The bond connecting two carbons is formed by the presence of a sp^2 hybrid orbital. Due to the energy supply during photon irradiation it changes to a sp^3 hybrid orbital and becomes weaker. This transformation records monomer consumption which is present when radiation induced gel polymerization process starts. In general monomer consumption lead to the reduction of the vibrational mode intensity with the increasing dose, however the overall peak intensity does not drop to zero, especially at low irradiation doses, since a certain amount of monomer is still left

in the gel after irradiation. Another band used for verification of monomer transformation to polymer was caused by C=C stretching vibrational mode and was observed at 1687 cm^{-1} [7, 16]. A C=C double bond changes to a single C-C bond when polymerization proceeds and is followed by the gradual decrease of the vibrational mode intensity. The identification of this C=C Raman peak might be complicated since the broad band ($1200\text{ cm}^{-1} - 2500\text{ cm}^{-1}$) corresponding to gelatin and its constituents in gels can overlap it. This problem was not acute analyzing photon irradiated gels since well-established Raman peak at 1687 cm^{-1} was found in all analyzed nMAG gels irradiated to different doses. It was decreasing smoothly with the increasing radiation dose, indicating effective consumption of monomer. Spectral information regarding photon induced polymerization behavior of methacrylic acid was also obtained analyzing intensive band appearing at 2937 cm^{-1} , which was assigned to symmetric vinyl stretching mode $\nu(\text{CH}_2)_s$. This vibrational mode is the only one which does not overlap with other bands [16] thus providing “true” information about polymerization process. The peak at 1450 cm^{-1} (figure 3) most probably may be attributed to the CH_2 vibrational bending mode of polymethacrylic acid (PMAA). As expected the intensity of this band was increasing with the increasing photon irradiation dose, since it records formation of polymeric structure.

3.2. Evaluation of proton irradiated nMAG gels using Raman spectroscopy.

A weak peak at 771 cm^{-1} corresponding to symmetric stretching mode of C-COOH was observed in proton irradiated gels (figure 4). Since the location of this peak was also altering with a dose, it was impossible to provide evidence based statement regarding monomer consumption in proton irradiated nMAG gels using this particular band. Decreased intensity of the 1695 cm^{-1} peak was attributed to the C=C stretching vibrational mode changes to a single C-C bond. Only modest changes of 1695 cm^{-1} peak intensity with the increasing dose were observed due to the waste contribution of the overlapping “gelatin” band. Well-expressed peak at 2940 cm^{-1} , which was assigned to symmetric vinyl stretching mode $\nu(\text{CH}_2)_s$, was the only one which clearly indicated peak intensity decrease with the increasing dose thus allowing the evaluation of monomer consumption due to polymerization in proton irradiated nMAG gels. However a sharp peak was observed only for initial gels. It became broader after irradiation indicating formation of a number of polymer radical chains that favor a faster termination of the polymerization reactions. A band with modest increasing Raman peak intensity due to increase of irradiation dose was found at 1410 cm^{-1} . It was assigned to the CH_2 vibrational bending mode of PMAA, whose changes record formation of polymeric structure.

3.3. Tendencies of monomer consumption /polymer production in irradiated nMAG gels.

The tendencies for monomer consumption and polymer production in photon and proton irradiated nMAG gels are provided in figure 5 and figure 6 respectively.

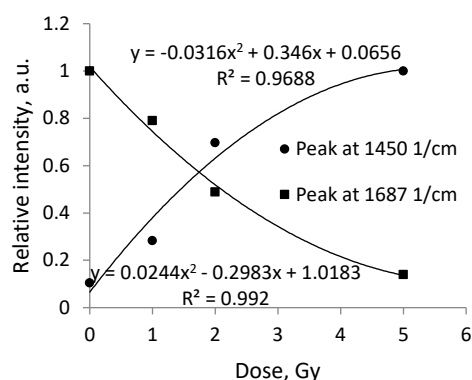


Figure 5. Monomer consumption (peak at 1687 cm^{-1}) and polymer formation (peak at 1450 cm^{-1}) in photon irradiated nMAG gels.

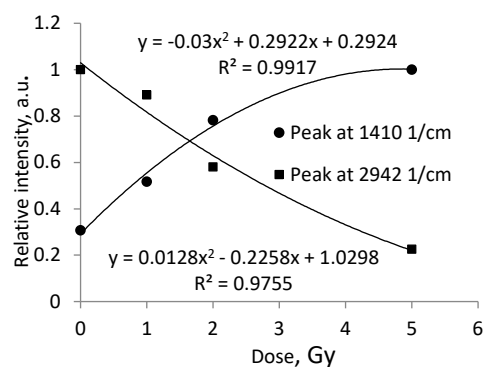


Figure 6. Monomer consumption (peak at 2942 cm^{-1}) and polymer formation (peak at 1410 cm^{-1}) in proton irradiated nMAG gels.

Investigation revealed that even at low irradiation doses monomer consumption and polymer formation processes in irradiated gels were not following linear tendency. It was found that monomer consumption and polymer formation rates were almost the same in photon irradiated gels and were slightly higher than those estimated for proton irradiated gels. This indicates relative higher dose sensitivity of nMAG gel to irradiation with 15 MeV photons.

Faster consumption of monomer as compared to polymer production in proton irradiated gels was observed. It was explained by the fact that polymerization takes place very locally in the vicinity of proton path. Due to the high LET, monomer consumption in proton irradiated nMAG gels is not uniform (figure 6). The relative intensity of characteristic Raman peaks drops down due to the significant changes in the bonding structure of dose gels along the high energy proton track and possible local polymerization. However not all proton irradiation produced chemical fragments are tending to form polymeric chains. Some of them may participate in a reverse process of monomer formation since a large number of produced fragments are concentrated very locally. Dose (absorbed energy) dependent competing processes: polymerization and monomer formation contribute to the overall modest polymer formation rate as compared to monomer consumption.

4. Conclusions

Performed investigation revealed that the advanced nMAG gels containing 8% of methacrylic acid and 6% of gelatin were sensitive enough to assess gel polymerization caused by low dose photon and proton irradiation, however proton irradiated gels were less sensitive to irradiation due to the specific high LET proton interaction processes within gels. It was found that even at low irradiation doses polymerization level was not linearly increasing with the increasing dose. Monomer consumption and polymer production rates were almost the same in photon irradiated gels. In the case of proton irradiation monomers were destroyed (breaking of carbon double bonds) relatively fast, but not all chemical fragments were tending to form polymer chains. Presence of two competing processes in proton irradiated gels: monomer formation and polymerisation, led to for relative modest polymer formation rate. The reverse process of monomer formation was possible due to the fact, that a large number of radicals were produced very locally in the nearest vicinity of proton tracks.

5. Acknowledgements

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