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The quenching effect in PRESAGE® by a proton beam: Investigation of formulation dependence

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Abstract: The radiochromic dosimeter PRESAGE® has shown potential in conventional radiotherapies, but it suffers from dose under-responding, or signal quenching, in proton therapy as a result of dependence on variations in the linear energy transfer (LET). Early investigations have shown the under-response is affected by the chemical concentration of the active components, but as yet this relationship has not been comprehensively measured. This study investigated the impact of PRESAGE® formulation changes on signal quenching to determine the magnitude by which the quenching can be minimized.

1. Background

Radiotherapy techniques have advanced significantly over the last two decades and dose planning has also become significantly more complex [1-3]. This is explicitly seen in proton therapy, which includes extremely steep dose gradients as a result of the Bragg peak. Conventional QA for complex field arrangements is performed using point dose measurements (usually ionization chamber) or planar systems (film and diode arrays) that are limited in their ability to record such gradients. Additionally, using conventional dosimetry systems to fully characterize complex dose distributions can be labor intensive. In 2015, an IROC-H phantom study showed that over 20% of participating proton institutions failed credentialing criteria, indicating that beam commissioning might have been inadequate [4]. A 3D dosimetry system could provide comprehensive volume measurements that are captured in a single irradiation and can potentially catch planning and delivery errors missed by conventional dosimetry systems.

PRESAGE® (Heuris Pharma, LLC, Skillman, NJ), a radiochromic polyurethane, is a three-dimensional (3D) dosimeter that has distinct advantages over many other 3D alternatives such as improved thermal and temporal stability, environmental robustness, and improved measurement accuracy through optical-CT imaging. The active ingredients in PRESAGE® that result in the dose signal are a halocarbon radical initiating activator and a leuco dye reporter which, when irradiated, undergoes a measureable darkening of color. Previous studies have demonstrated PRESAGE® can be successfully used to measure complex photon dose distributions [5-8].

Unfortunately, PRESAGE® suffers from a dose under-response, or signal quenching, in the Bragg peak region, making accurate proton dosimetry so far impossible [9-11]. This signal quenching has also been observed in polymer gels as well as most other 3D dosimetry alternatives and the source has been primarily attributed to LET-dependence [12]. Early proton irradiations in polymer gels found

that high-LET dose deposition resulted in recombination of the radical initiators rather than signal activation resulting in dose under-response [13], local depletion of the signaling components [14], or some combination of the two. While conventional PRESAGE® irradiated with protons demonstrated maximum quenching greater than 30%, a newer formulation developed specifically for proton therapy was developed by Heuris Pharma, LLC which adjusted the concentrations of the active components. Our studies with this formulation measured a 20% under-response [15].

No known studies have comprehensively investigated relative concentrations of the radical initiator and leuco dye responder to chemically correct for PRESAGE® signal quenching in a proton beam. In this study, we investigated the relationship of the radical initiator component on LET-dependence to assess the potential of a formulaic correction of this quenching effect.

2. Methods and Materials

2.1 PRESAGE® Manufacturing

The PRESAGE® dosimeters used in this study were manufactured in-house using the chemical components described previously: Leuco Malachite Green (LMG) dye, chloroform ($CHCl_3$) radical initiator, dibutyltin dilaurate as a catalyst, and polyurethane resin (Parts A and B, Crystal Clear 204, Smooth-On). Ten formulation batches were made with radical initiator concentrations varying between 3.0-30.0% (w/w) using a method described by Alqathami *et al* [16]. A static 2.0% (w/w) LMG concentration was used in all formulations. The total polyurethane concentration between formulations was adjusted for changes to radical initiator concentration. Parts A and B maintained a 10:9 ratio as recommended by the supplier. The catalyst concentration was <<1% (w/w). After combining all ingredients, the formulations were poured into spectrophotometer cuvettes (1x1x4.5 cm^3) then placed in a pressure chamber and allowed to cure for 24 hours at 70 psi to eliminate the formation of air bubbles.

2.2 Irradiation

The cuvettes were irradiated using a 225-MeV (26.9 cm range) passively scattered proton beam at the MD Anderson Proton Therapy Center (MDACC PTC, Houston, TX). The beam was modulated to deliver a 10 cm SOBP with a 10x10 cm^2 field size. A solid water phantom was used and cuvettes were positioned at four depths along the beam profile. The first depth was 10 cm and situated in the low LET dose plateau allowing dose normalization. Cuvettes were next irradiated at three points along the SOBP at the following depths to measure a uniform dose at varying LETs: 19 cm (the most proximal SOBP region), 22 cm (SOBP center), and 25 cm (the distal most SOBP region). Two cuvettes were independently irradiated at each position for each formulation. The cuvettes were irradiated to 193.6 MU (approximately 200 cGy to the SOBP). The beam profile was separately measured using a Zebra multilayer ion chamber (MLIC). Additionally, the dose-averaged LET (LET_d) was calculated analytically using a model developed by Wilkens *et al* [17].

2.3 Readout

The dose signal was measured by the change in optical density (ΔOD) of the cuvettes using a Thermo Scientific GENESYS™ 10S UV-VIS spectrophotometer. Optical measurements were made at the absorption peak wavelength of 632 nm approximately 24 hours after irradiation. The ΔOD was determined by subtracting the pre-irradiation measured OD from the post-irradiation measured OD. Cuvettes were protected from light exposure at all times and stored in a cold environment (<3°C) except when allowed to equilibrate to room temperature two hours prior to measurements and irradiation.

The ΔOD for each formulation was normalized to dose using the average of the measurements from cuvettes in the dose plateau region to the dose measured by the MLIC. The quenching magnitude for the measurements along the SOBP region was calculated as the difference of the normalized PRESAGE® signal to the ion chamber measurements made at each depth.

3. Results

Figure 1a shows the normalized dose responses of each PRESAGE® formulation relative to ion chamber measurements. All formulations demonstrated quenching along the SOBP. Figure 1b shows the magnitude of the quenching for better illustration. Formulations with radical initiator concentrations between 12-21% under-responded by less than 3% at the proximal SOBP dose point. The quenching magnitude for these concentrations increased slightly at the other measurement points. Formulations outside of this range had greater quenching magnitudes across all points. The 12% $CHCl_3$ formulation showed the lowest quenching across the whole dose profile with a maximum under-response of 14.6%. In contrast, the 30% $CHCl_3$ formulation showed a maximum under-response of 73.8%.

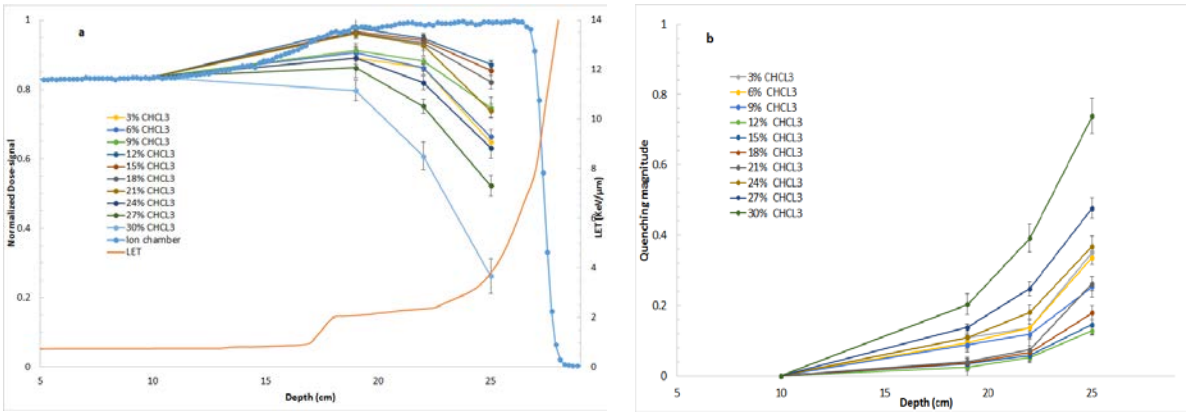

Figure 1. (a) The normalized dose-response curves for each PRESAGE® formulation irradiated by a proton beam compared with ion chamber measurements. The pointes are connected by straight lines to aid the eye. Additionally, the calculated LETd is illustrated. (b) Only the magnitude of the quenching is shown as a function of depth.

The calculated LET_d is shown in Figure 1a. Figure 2a correlates the quenching magnitude with the LET_d at each point. PRESAGE® formulations with radical initiator concentrations below 12% or above 18% demonstrated sharper quenching increase than intermediate concentrations. This resulted in a kind of minimized quenching plateau of similarly responding formulations between 12-18% in the lower LET measurement points. The relationship between dose quenching and LET_d is plotted in Figure 2b. This unexpectedly shows a linear relationship in formulations between 3-21% which becomes sublinear at higher radical initiator concentrations.

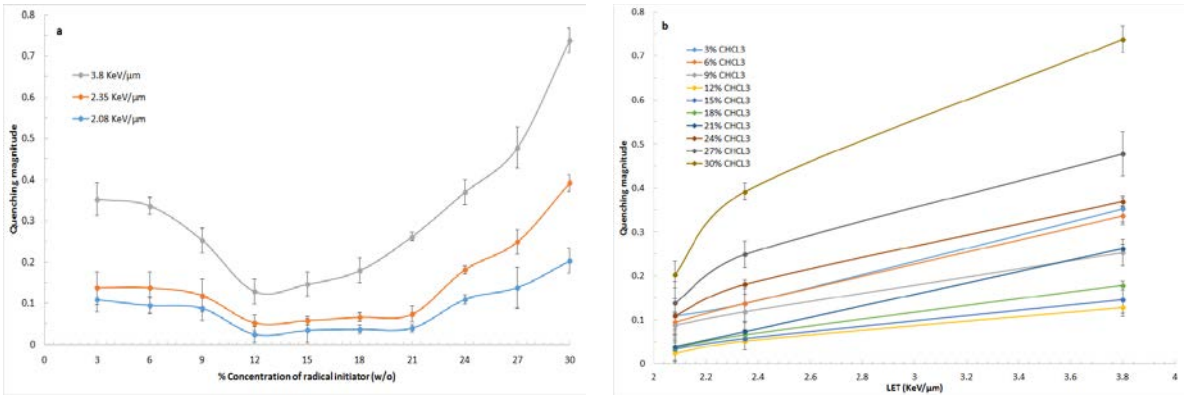

Figure 2. (a) The quenching magnitude at each measured LETd as a function of radical initiator concentrations. (b) The quenching as a function of LETd for each PRESAGE® formulation.

4. Discussion and Conclusions

The concentration of the radical initiator in PRESAGE® dosimeters is shown to affect the magnitude of the dose quenching in a proton beam. Unfortunately, a limit to this quenching reduction was reached before it could be fully eliminated, but this is sufficient to demonstrate that further formulation optimization can improve the standard proton formulation available today.

This study also offers some insight into the physical processes resulting in quenching. As radical initiator concentrations increase beyond a point, the quenching magnitude begins to sharply increase which demonstrates that radical recombination likely plays a role in the quenching effect, although it may not be the only contributor. Further studies are needed to determine the impact on quenching from leuco dye saturation as well as to determine if the quenching can be further reduced with chemical substitutions.

5. References

[1] Klein E E *et al* 2009 *Med. Phys.* **36** 4197-212
[2] Hill R *et al* 2009 *Med. Phys.* **36** 3971-81
[3] Hill R *et al* 2014 *Phys. Med. Biol.* **59** R183-231
[4] Summers P *et al* 2013 *Med. Phys.* **39** 3866
[5] Klawikowski S J *et al* 2014 *Phys. Med. Biol.* **59** N211-20
[6] Juang T *et al* 2014 *Med. Phys.* **41** 071706
[7] Grant R *et al* 2013 *J. Phys.: Conf. Ser.* **444** 012020
[8] Wuu C-S *et al* 2013 *J. Phys. Conf. Ser.* **444** 012055
[9] Zhao L et al 2010 *J. Phys.: Conf. Ser.* **250** 12035
[10] Gorjiara T *et al* 2011 *Med. Phys.* **38** 2265-74
[11] Zhao L *et al* 2012 *Phys. Med. Biol.* **57** N431-43
[12] Karger C P *et al* 2010 *Phys. Med. Biol.* **55** R193-234
[13] Gustavsson H *et al* 2004 *Phys. Med. Biol.* **49** 3847-55
[14] Schmid A I *et al* 2013 *J. Phys.: Conf. Ser.* **444** 012096
[15] Carroll M *et al* 2013 *J. Phys.: Conf. Ser.* **444** 012059
[16] Alqathami M A *et al* 2016 *Phys. Med. Biol.* **61** 813-24
[17] Wilkens J J and Oelfke U 2003 *Med. Phys.* **30** 806-15