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Locally targeted delivery of a micron-size radiation therapy source using temperature-sensitive hydrogel

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Abstract

Purpose—To propose a novel radiotherapy (RT) delivery modality—locally targeted delivery of micro-size level RT sources using temperature-sensitive hydroGEL (RT-GEL) as an injectable vehicle.

Methods and Materials—Hydrogel is a water-like liquid at room temperature but gels at body temperature. Two FDA-approved polymers were synthesized. Indium-111 (In-111) was used as a radioactive RT-GEL source. The release characteristics of In-111 from polymerized RT-GEL were evaluated. The injectability and efficacy of RT-GEL delivery to human breast tumor were tested using animal models with control datasets of RT-Saline injection. As proof-of-concept studies, a total of 6 nude mice were tested by injecting 4 million tumor cells into their upper backs after a week of acclimatization. Three mice were injected with RT-GEL and three with RT-Saline. A SPECT and a CT scan were performed on each mouse at 0, 24, and 48 hours after injection. The efficacy of RT-GEL over the control datasets was determined by measuring kidney In-111 accumulation (mean nCi/cc), representing the distant diffusion of In-111.

Results—RT-GEL was successfully injected to the tumor using 30-gauge needles. No difficulties due to polymerization of hydrogel during injection and intratumoral pressure were observed during RT-GEL injection. No back flow occurred for either RT-GEL or RT-Saline. The residual tumor activities of In-111 were 49% (44%) at 24 hours (48 hour) for RT-GEL and 29% (22%) for RT-Saline. SPECT-CT fused images of RT-Saline show considerable kidney accumulation of In-111 (2,886%, 261% and 262% of RT-GEL at the 0, 24 and 48 hour marks, respectively).

Conclusion—RT-GEL was successfully injected and showed much higher residual tumor activity 170% (200%) than that of RT-Saline 24 hour (48 hour) after injection with a minimal

accumulation of In-111 to the kidneys. The preliminary data of RT-GEL as a delivery modality of a radiation source to a local tumor is promising.

Keywords

Local targeted radiotherapy; temperature-sensitive hydrogel; ablation radiotherapy

I. Introduction

Local targeted injection of therapeutic agents has been tried without success because of difficulties with back-flow and immediate-uncontrollable diffusions of toxic therapeutic agents. In order to diminish these problems we synthesized a temperature-sensitive hydrogel (GEL) for use as an injectable vehicle to deliver microspheres of a therapeutic-agent (drug or stem cells) (see Figure 6 of (1)). The GEL exists in two states: a water-like fluid at low temperature and a polymerized gel at body temperature (37°C) (see Figure 5 of (1)). When injected, the solution gels almost instantaneously at body temperature, preventing back-flow during injection and the immediate release of microspheres. In a previously published study (1), GEL was developed and tested to deliver solid microspheres of pain control medication to bovine lumbar spinal motion segments. It was found that the delivery of therapeutic microspheres through percutaneous injection was possible.

In this study, we propose *delivering local high-dose radiation therapy (RT) using micron or smaller sized radiation sources embedded into temperature-sensitive hydrogel (RT-GEL)*. Clinical evidence suggests that local tumor control can be enhanced using radiation dose boost techniques for head-and-neck (2), prostate (3), lung (4), liver (5), and breast cancers (6). Brachytherapy is the treatment of choice to deliver local high-dose radiation to the tumor with minimal radiation dose delivered to the adjacent healthy tissues. However, its radiation conformality is limited by the source size (~5 mm). The smaller size of RT-GEL has potential to allow for better local uniform dose distribution over currently used brachytherapy sources. Consequently RT-GEL can be injected through a needle or be delivered through any RT-GEL filled, shaped applicator.

II. Method and Materials

A. Temperature-sensitive hydrogel

The GEL consisted of two FDA-approved polymers, Pluronic® F-127 (F-127; BASF, Gurney, IL; MW: 12.6 KDa) and animal-free sodium hyaluronate (SH; Shiseido, Japan; MW: 1.9-2.7 MDa). The final concentration of F-127 and SH was 20% (w/v) and 0.4% (w/v), respectively. More than 79% of polymerized GEL is composed of water so the GEL is not expected to retain molecules such as Indium-111 (In-111) through the gelation life-time. The GEL half-life is 3 days. In a previous study (1), the effect of each F-127 (see Figure 2 of (1)) and SH concentration (see Figure 3 of (1)) on the viscosity and temperature relationship were tested, and their final concentration was used in this study. The cytotoxicity and biocompatibility of the GEL were first tested *in-vitro* in accordance with International Standards for Organization standards and in *in-vivo* using rat models (7). The GEL is biodegradable and its physical properties and gelation characteristics were previously described in detail (1). Generally, a hydrogel, that gels *in situ* with an increase in

temperature, occurs when the triblock PEO (polyethylene oxide)-PPO (polypropylene oxide)-PEO copolymer is added to sodium hyaluronate by mechanical mixing (8). In order to test if the GEL could be reliably injected into a pressurized space like a cancer mass, we first injected the GEL loaded with microspheres and BaSO₄ into the bovine intervertebral disc as described in the previous study (1). As shown in Figure 1 of (1), injecting the microsphere GEL into the disc was reliably accomplished without backflow, but this was not the case when delivered using the saline solution. The GEL was biocompatible with the stem cells residing in it (7). We also found that the stem cells can be loaded into the GEL in fluid phase at low temperature without using microspheres. In this study, the GEL injectability was tested by injecting stem cells into the rat intervertebral discs using a 27 gauge syringe. The stem cells delivery using saline was used as the control dataset. The delivered stem cells were evaluated with fluorescent imaging and qualitatively compared between GEL and saline based delivery.

B. In-111 release characteristics from temperature-sensitive hydrogel

To introduce GEL to the field of radiation therapy, we first synthesized RT-GEL using In-111, and tested the radiation effects and release characteristics of In-111 from polymerized RT-GEL (Figure 1 B) embedded in phosphate-buffered saline. The half-life of In-111 is 2.8 days and its primary gamma ray energy is 862 keV. In-111 has a smaller molecular size when compared to other potential radioactive sources using the RT-GEL technique. As a proof-of-concept study, In-111 was used instead of microsphere-Y90 for two reasons: the prohibitive cost of microsphere-Y90 (1 vial (81 mCi/5mL) / \$15,000) and that the beta emitter characteristics of Y90 are not detectable on SPECT. In-111 is not embedded in glass-microspheres, so In-111 was diluted in 0.1N HCL and 0.01 ml In-111/HCL (initial dosage; 154.1-186.9 μ Ci) and then mixed with 0.09 ml GEL, formulating RT-GEL. The 0.1 ml of the final RT-GEL mixture was moved to a 1.5 ml centrifuge tube and polymerized completely in a 37°C chamber. The 1 ml phosphate-buffered saline was added to the tube. Polymerized RT-GEL is located at the bottom of the centrifuge tube while the phosphate-buffered saline, occupies the upper layer. To evaluate In-111 release characteristics, the centrifuge tube was shaken with a speed of 400 rpm. In phosphate-buffered saline, the amount of released In-111 from the polymerized RT-GEL was measured using an Atomlab chamber (Biodex Medical Systems, Shirley, NY) at various time points until 50 hours had elapsed.

C. Injectability and efficacy of RT-GEL

The feasibility of RT-GEL delivery to human breast tumors was determined through the testing of its injectability within the tumor microenvironment under intratumoral pressure. The tumor is at body temperature, so the polymerization of RT-GEL during injection was also investigated. RT-GEL's efficacy was evaluated using the control datasets of the RT-Saline injection. As a proof-of-concept study, six nude mice were injected with 4 million tumor cells (luciferized MDA-MB-231) in their upper backs after a week of acclimatization (Figure 3 A). The RT-GEL or RT-Saline was injected using 30-gauge needles. We synthesized the RT-GEL and RT-Saline using 0.5 mCi In-111 in 0.1 mL volume of the GEL and the saline, respectively (Figure 3 B). RT-GEL was injected into three of the mice, while RT-Saline was injected into the other three. We aimed for the center of tumor when

injecting the 0.1 mL of RT-GEL or RT-Saline using a single injection (Figure 3 C). In order to avoid potential polymerization before the injection, the liquid RT-GEL was kept on ice until it was ready to be injected into each mouse. The time taken for the injection was similar for both RT-GEL and RT-Saline. SPECT and CT datasets of all six mice were obtained using an animal SPECT/CT scanner (Siemens Medical Systems, Erlangen, Germany) at our institutional Small Animal Imaging Core (SAIC) (Figure 3 D). CT provided a field of view up to 10 cm × 10 cm with an automated zoom for optimizing the field of view and resolution to 20 microns. Whole mouse SPECT scanning was possible using gamma rays ranging in energy from 30 to 300 keV. The imaging system provided fused 3D SPECT/CT datasets of CT and SPECT scan. Both scans for each mouse were performed at 0, 24, and 48 hour intervals. Here “0” hour refers the scans immediately after injection. We evaluated the efficacy of the RT-GEL over the control datasets using kidney In-111 accumulation, representing distant diffusion of In-111. The tumor and the kidney were contoured on CT datasets and their volumes estimated. The tumor sizes on the upper backs of the mice were also measured at 0, 24, and 48 hour intervals using a caliper (Figure 3 A). The In-111 activities (nCi/cc) on the tumor and the kidney were measured using SPECT datasets. To compare the RT-GEL with the RT-Saline (Control), tumor activity at 24 and 48 hours was normalized to that occurring at 0 hours. Kidney activity was measured for both right and left kidneys.

II. Results

Stem cells (green color) were successfully injected into the pressurized space of an intervertebral disc using a 27-gauge needle without any back flow observed (Figure 1). The whole injected stem cell volume coalesced in the center of the disc (Figure 1 A, fluorescent green) when injected using the GEL. In contrast, almost all of the stem cells were dispersed throughout the saline solution and were found outside of the disc (Figure 1 B, fluorescent green) due to the intradiscal pressure pushing the saline solution containing stem cells out of the disc and into the needle tract during injection.

Afterwards, In-111 release characteristics from polymerized RT-GEL were validated (Figure 2). The release of In-111 was observed in the first 10 hours (up to $52\% \pm 2.5\%$) with slower release occurring at later time points ($75.3\% \pm 4.7\%$ after 2 days).

RT-GEL was successfully injected into the breast tumor sites of three mice using 30-gauge needles, demonstrating favorable injectability of RT-GEL to the tumor. No noticeable polymerization effect during the injection of RT-GEL occurred. RT-GEL injection was not very different from RT-Saline. For both cases the injection time was less than 2 minutes and no back flow was noticed. Average tumor size at 0, 24, and 48 hour time points were 10.8 ± 0.8 mm, 7.1 ± 2.4 mm, and 4.8 ± 3.2 mm, respectively when measured using a caliper (Figure 3 A). Based the contours on CT, mean tumor volumes of all mice were 0.37 ± 0.07 cc, 0.29 ± 0.12 cc (-23% volume reduction), and 0.24 ± 0.11 cc (-35%) at 0, 24, and 48 hour time points, respectively. Mean tumor volume reductions of RT-GEL (RT-Saline) groups were $-23 \pm 21\%$ ($-19 \pm 20\%$) and $-44 \pm 26\%$ ($-22 \pm 14\%$) at 24 and 48 hour time points, respectively.

Figure 4 A shows, a fused SPECT-CT image of RT-Saline (Control) exhibiting considerable kidney accumulation of In-111 whereas the RT (In-111)-GEL (Sample) shows minimal kidney accumulation of In-111. RT-GEL showed higher residual activity on the tumor, an average of 170% at 24 hours and an average of 200% at 48 hours when compared to those of RT-Saline (Figure 4 B). RT-Saline, showed vastly higher kidney accumulations of In-111, an average 2886% at 0 hour, an average of 261% at 24 hours, and an average of 262% at 48 hours. The vast amounts of radiation dose from RT-Saline were delivered to the kidney, while the radiation dose of RT-GEL was delivered mainly to the local-targeted tumor regions.

III. Discussion

To the best of our knowledge, this is the first study to examine the delivery of radiation source using temperature-sensitive hydrogel. The use of hydrogel was introduced in radiotherapy to act as a spacer between the rectum and the prostate (9, 10) or as a radiopaque marker (known as fiducials) (11) for advanced MRI-guided radiotherapy such as VIEWRAY (ViewRay System Inc., Oakwood Village, Ohio).

One of the limitations of Y90 as a radioactive source when using the RT-GEL technique is that the beta emitter characteristics of Y90 are not detectable on SPECT. Y-90 microspheres have been widely used in selective internal radiotherapy (SIRT) for hepatic malignancies. The direct imaging of Y-90 using SPECT or PET-CT has gained interest for use in direct 3-D dosimetry using these imaging modalities even though research is still at an early stage (12-15). SPECT imaging can be tested to determine if it is able to detect bremsstrahlung radiation from high activity Y-90, for example, 5 mCi on mice skin (16). The decay of Y-90 shares a minor positron branch to the first excited state of Zr-90 (a rare positron emission) yet is still observable on a PET scan (15). Fourkal *et al.* (15) found the 3-D dose reconstruction from the PET-CT imaging of Y-90 microspheres was feasible, showing potential for significant improvement in the characterization of the Y-90 dose distribution. As a surrogate for Y-90 distribution, BaSO₄ dummy-microsphere markers can be mixed with Y-90 microspheres in the RT-GEL.

The release speed of In-111, up to 52% in the first 10 hours, could be mainly caused by the smaller molecular size of In-111 when compared to other potential radiation sources. In-111 is molecular in size while microsphere-Y90 is about 20 - 30 microns in size. The larger microsphere-Y90 are expected to release slower from polymerized RT-GEL as the polymerization is degraded when compared to the smaller In-111. Another benefit of using microsphere-Y90 is chemical reaction stability. The tumor microenvironment parameters such as intratumoral pressure, oxygenation, and pH could be altered by the RT-GEL and its radiation source injection. Follow up studies will examine the distribution of microsphere-Y90 within the polymerized RT-GEL to evaluate the uniformity of radioactive sources within the GEL. The release characteristics of microsphere-Y90 from polymerized RT-GEL will also need to be quantified.

RT-GEL showed higher residual activity of In-111 at 24 and 48 hour time points within the tumor than RT-Saline did. However, an average tumor activity reduction of 51% (71%) was

observed for RT-GEL (RT-Saline) within 24 hours. These findings were partly due to the fact that the RT-GEL or RT-Saline volume of 0.1 ml, was relatively large (~27%) when considering tumor volume (0.368 ± 0.07 ml) at 0 hour. The whole volume of RT-GEL or RT-Saline (0.1 ml) may not have fit within tumor. The use of microsphere-Y90 is expected to improve the local distribution of RT-GEL in the tumor even if some microsphere-Y90 are located at or outside of the tumor boundary. The polymerized gelation level is changed by modifying the composition of the hydrogel, along with its gelation half-life. Changes in gelation level and gelation half-life are linked with the changes in the toxicity of polymerized hydrogel. Thus, the biocompatibility of new hydrogels must be validated before starting clinical trials.

In a previous injectability study (1) of therapeutic microspheres injected with a saline solution into a pressurized region (the intervertebral disc), the therapeutic microspheres delivered using saline were flowed back out of the intervertebral disc (see Figure 6 in (1)). In this study, no back flow was observed for both RT-Saline and RT-GEL. No difficulties due to early polymerization during injection were observed. RT-GEL groups presented larger tumor volume changes (-44%) at the 48 hour mark than the RT-Saline (-22%) but their small sample size is too small to evaluate statistical significance. The therapeutic efficacy of RT-GEL will be quantified using a larger sample size. Potential clinical applications of RT-GEL include the treatment of unresectable hepatic malignancies. This along with the transarterial administration of microsphere-Y90 is a SIRT (17, 18) for which there are two FDA-approved microsphere-Y90 devices (Thera-Sphere®, MDS Nordion, Ottawa, Ontario, Canada and SIR-Spheres®, Sirtex Medical, Sydney, Australia). The direct local injection of RT-GEL with microsphere-Y90 to the target region of the liver has the potential to improve the distant accumulation of Y-90. RT-GEL may also be used as an alternative technique for radiofrequency ablation therapy (19) or stereotactic body radiotherapy for painful bone metastases (20). In this study, the tumor sizes were relatively small (on average 0.37 mL), compared to that of cancer patients and the tumor was superficially located on the back of nude mice. The amount of RT-GEL used in this study was accordingly small (0.1 mL) and the needle track embedded in body-temperature tissue was short. These favorable conditions for RT-GEL injection are expected to change significantly in human applications. For instance, the tumor is not superficially located on the skin. For interstitial brachytherapy, 15 – 18 gauge (1.83 – 1.3 mm diameters) needles are typically used. For liver (21) and adrenal gland (22) high-dose-rate (HDR) brachytherapy, 16 gauge and 18 gauge needles, respectively, are used which have a much greater diameter than the needles used in this study. The issues of backflow and polymerization, when RT-GEL is used with in a relatively larger volume and delivered through a bigger needle, should be characterized in the environment of potential clinical sites.

The selection of the radioactive source for the RT-GEL technique -especially its energy and range- should be optimized according to the clinical application of RT-GEL. It can be also used in pad or balloon shape applicators. When using the GEL as a delivery vehicle, therapeutic agents such as stem cells or chemotherapy drugs can be delivered through needle injection. The RT-GEL experiments using either In-111 or Y-90 microspheres should follow state and federal radiation safety rules. For instance, experiments must be performed in a laboratory equipped and licensed to handle radioactive materials and by experienced

personnel licensed handle radioactive materials. In this proof-of-concept study, low activity (initial dosage; 154.1-186.9 μ Ci) was used. Depending on the activity and the energy of radioactive sources for RT-GEL technique, the use of lead-coated gloves or tongs should be strongly considered.

IV. Conclusion

Using 30-gauge needles, RT-GEL was successfully injected into human breast tumors on mice without encountering the difficulties associated with intratumoral pressure and polymerization during injection. RT-GEL showed much higher residual tumor activity 170% (200%) than RT-Saline at 24 hour (48 hour) after injection. RT-GEL also presented minimal accumulation of In-111 in the kidneys. RT-Saline showed 2,886% and 261% higher In-111 accumulation than RT-GEL at the 0 and 24 hour time points. As a proof-of-concept study, the preliminary data of RT-GEL as a delivery modality of a radiation source to a local tumor is promising.

References

1. Lee JW, Lim TH, Park JB. Intradiscal drug delivery system for the treatment of low back pain. *Journal of biomedical materials research Part A*. 2010; 92:378–385. [PubMed: 19191317]
2. Marks JE, Bedwinek JM, Lee F, et al. Dose-response analysis for nasopharyngeal carcinoma: an historical perspective. *Cancer*. 1982; 50:1042–1050. [PubMed: 7104948]
3. Hanks GE, Hanlon AL, Schultheiss TE, et al. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys*. 1998; 41:501–510. [PubMed: 9635695]
4. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys*. 2005; 63:324–333. [PubMed: 16168827]
5. Dawson LA, McGinn CJ, Normolle D, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol*. 2000; 18:2210–2218. [PubMed: 10829040]
6. Dale RG, Jones B, Price P. Comments on Inadequacy of iridium implant as sole radiation treatment for operable breast cancer, Fentiman et al., *Eur J Cancer* 1996, 32A, pp. 608-611. *European journal of cancer*. 1997; 33:1707–1708. [PubMed: 9389938]
7. Seol DR, Magnetta MJ, Ramakrishnan PS, et al. Biocompatibility and preclinical feasibility test of a temperature sensitive hydrogel for the purpose of surgical wound pain control and cartilage repair. *J Biomedical Materials Research Part B: Applied Biomaterials*. 2013 In Press.
8. Cohn D, Sosnik A, Levy A. Improved reverse thermo-responsive polymeric systems. *Biomaterials*. 2003; 24:3707–3714. [PubMed: 12818542]
9. Susil RC, McNutt TR, DeWeese TL, et al. Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010; 76:1251–1258. [PubMed: 19939577]
10. Pinkawa M, Corral NE, Caffaro M, et al. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol*. 2011; 100:436–441. [PubMed: 21963289]
11. de Souza Lawrence L, Ford E, Gilbert C, et al. Novel applications of an injectable radiopaque hydrogel tissue marker for management of thoracic malignancies. *Chest*. 2013; 143:1635–1641. [PubMed: 23287908]
12. Paxton A, Nickles R, DeWerd L. Activity Assay of a Y-90 Microsphere Sample Using a Coincidence Detection System. *Med Phys*. 2012; 39:3856.

13. Gates V, Salem R, Spies S. Improved Technique for Determining Y-90 Glass Microspheres Activity Delivered. *Med Phys.* 2008; 35:2737.
14. A P, Owen R. Evaluation of Quantitative Direct PET/CT Imaging of Y-90 Microspheres Using the Jaszczak Phantom. *Med Phys.* 2011; 38:3436.
15. Fourkal E, Velchev I, Koren S, et al. 3D In-Patient Dose Reconstruction from the PET-CT Imaging of Y-90 Microspheres for Metastatic Cancer to the Liver. *Med Phys.* 2012; 39:3932.
16. Qian W, Clarke LP. A resoration algorithm for P-32 and Y-90 bremsstrahlung emission nuclear imaging: A wavelet-neural network approach. *Med Phys.* 1996; 23:1309. [PubMed: 8873028]
17. Gulec SA, Pennington K, Wheeler J, et al. Yttrium-90 Microsphere-selective Internal Radiation Therapy With Chemotherapy (Chemo-SIRT) for Colorectal Cancer Liver Metastases: An In Vivo Double-Arm-Controlled Phase II Trial. *Am J Clin Oncol.* 2012; 36:455–460. [PubMed: 22643569]
18. Prompers L, Bucerius J, Brans B, et al. Selective internal radiation therapy (SIRT) in primary or secondary liver cancer. *Methods.* 2011; 55:253–257. [PubMed: 21964397]
19. Di Francesco A, Flamini S, Zugaro L, et al. Preoperative radiofrequency ablation in painful osteolytic long bone metastases. *Acta Orthop Belg.* 2012; 78:523–530. [PubMed: 23019787]
20. Toyota N, Naito A, Kakizawa H, et al. Radiofrequency ablation therapy combined with cementoplasty for painful bone metastases: initial experience. *Cardiovasc Intervent Radiol.* 2005; 28:578–583. [PubMed: 16059766]
21. Sharma DN, Thulkar S, Sharma S, et al. High-dose-rate interstitial brachytherapy for liver metastases: first study from India. *J Contemp Brachytherapy.* 2013; 5:70–75. [PubMed: 23878550]
22. Kishi K, Tamura S, Mabuchi Y, et al. Percutaneous interstitial brachytherapy for adrenal metastasis: technical report. *J Radiat Res.* 2012; 53:807–814. [PubMed: 22843376]

Figure 1.

Stem cells injected into the middle of rat intervertebral discs using the temperature-sensitivity hydrogel (GEL) (A) vs. saline (B) as a delivery vehicle. When the cells were suspended into the GEL and injected, the whole injected volume was found in the middle of the disc (A, fluorescent green). In contrast, almost all of the stem cells dispersed in saline solution were found outside of the disc (B, fluorescent green).

Figure 2.
In-111-release characteristics from RT-GEL are shown for 50 hours.

Figure 3.

Four million tumor cells were injected into each mouse upper back and the tumor size was measured (A). 100 μ L of RT-GEL or RT-Saline (500 μ Ci of In-111) was injected to total six mice using a 30-gauge needle (B-C). SPECT and CT scans were performed at 0 hour, 24 hour, and 48 hour (D). The time at 0 hour represents immediate scans right after injection.

Figure 4. SPECT-CT fused images show qualitative pharmacokinetics of RT-GEL (Sample) and RT-Saline (Control) (A). The tumor activities at 24 hour and 48 hour were presented when normalized to 0 hour (B). The average activities (nCi/cc) of right and left kidney were compared at 0 hour, 24 hour and 48 hour (C).