Localized Hyperthermia with Iron Oxide–Doped Yttrium Microparticles: Steps toward Image-Guided Thermoradiotherapy in Liver Cancer

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ABSTRACT

Purpose: To test whether iron oxide (IO)–containing yttrium aluminosilicate (YAS) microparticles (MPs) can generate localized therapeutic hyperthermia ($\geq$ 43°C) when injected intratumorally in an animal model of liver cancer and whether MP distributions could be visualized with magnetic resonance (MR) imaging.

Materials and Methods: Twenty-one Sprague–Dawley rats implanted with N1-S1 liver tumors were assigned to alternating magnetic field (AMF) exposure following intratumoral injection with IO-YAS MPs (n = 7), sham surgery (n = 7), or baseline iron quantification (n = 7). Three fiberoptic probes allowed spatial and temporal monitoring of temperatures during 24 minutes of AMF exposure. T2-weighted turbo spin-echo MR imaging was performed within 1 hour after the procedure to detect signal voids caused by IO-YAS deposition. Hematoxylin and eosin–stained pathologic slides were also obtained, and the presence of IO-YAS was evaluated with inductively coupled plasma optical emission spectroscopy.

Results: Following AMF exposure, intratumoral temperatures after IO-YAS MP injection achieved therapeutic hyperthermia whereas those after sham surgery did not (46.6°C ± 1.3 vs 36.8°C ± 0.4; $P < .0001$). Within the treated group, the normal hepatic parenchyma (NHP) and rectal temperatures were 37.4°C ± 0.9 and 36.5°C ± 1.0 ($P = .0809$) at the conclusion of AMF exposure, respectively. A T2-weighted signal void at the tumor site was observed in all seven treated animals, and intratumoral IO-YAS was visualized on subsequent histopathologic examination in each case. The mean ratio of tumor:NHP Fe concentrations attributable to IO-YAS MPs was 108:1.

Conclusions: AMF exposure of intratumoral IO-YAS MPs generates localized therapeutic hyperthermia in an animal model of liver cancer. MR detectability and potential for combination brachytherapy warrants further investigation for thermoradiotherapy in liver cancer.

ABBREVIATIONS

AMF = alternating magnetic field, HCC = hepatocellular carcinoma, ICP-OES = inductively coupled plasma optical emission spectroscopy, IO = iron oxide, MP = microparticle, NHP = normal hepatic parenchyma, RF = radiofrequency, SAR = specific absorption rate, TSE = turbo spin-echo, YAS = yttrium aluminosilicate

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Hyperthermia can serve to synergistically augment radiation sensitivity and even improve survival in the treatment of some cancers (1,2). Inhibition of cellular repair mechanisms, enhanced tissue oxygenation, delivery of reactive oxygen species, thermal sensitivity of S-phase cells, and increased lysosomal activity are among the posited sensitization mechanisms (3,4). The combination of hyperthermia and radiation therapy (thermoradiotherapy) has demonstrated significantly improved locoregional control versus radiation therapy alone for accessible tumors of the chest wall, cervix, rectum, and bladder, in addition to melanoma and head and neck tumors, despite the great variability in delivery and dosing strategies (5). Therefore, hyperthermia may enhance the efficacy of radioembolization procedures for primary liver tumors and metastases.

In 1957, Gilchrist et al (6) reported the use of 0.02–0.1-μm Fe_2O_3 particles for selective inductive heating of lymph nodes in dogs. Contemporary thermoradiotherapy combining magnetic hyperthermia of ferrofluids and external-beam radiation therapy was approved for clinical treatment of glioblastoma in the European Union (7) and is also being investigated for the treatment of prostate cancer, with promising initial results (8). This progress provides important evidence of clinical applicability that may facilitate targeted thermoradiotherapy in liver cancer through similar instrumentation.

The introduction of iron oxide (IO) as an integral component of embolic materials is appealing because it allows for (i) rapid and sustained localized heating of targeted tissues with noninvasive, external application of alternating magnetic fields (AMFs) (9), (ii) MR imaging of embolic material delivery (10), and (iii) enhanced retention of these materials within tumor tissues and/or vascular beds on external application of a static magnetic field (11,12). Yttrium aluminosilicate (YAS) microspheres with IO (ie, Fe_2O_3) nanocrystals dispersed throughout the glass matrix permit intraprocedural magnetic resonance (MR) imaging of intrahepatic biodistributions following transcatheter delivery (13).

The purpose of the present study was to test the hypothesis that magnetically functionalized YAS glass doped with magnetite (ie, Fe_3O_4) nanocrystals can generate AMF hyperthermia for applications in image-guided locoregional thermoradiotherapy (ie, radioembolization augmented with focal hyperthermia) and allow visualization with MR imaging. We evaluated the AMF heating properties of nonactivated (ie, yttrium-89) IO-YAS microparticles (MPs) in phantoms and demonstrated localized therapeutic hyperthermia ($\geq$ 43°C) and visualization with MR imaging when injected within deep-seated liver tumors in an animal model of liver cancer. A control group for the applied AMF was implemented to account for eddy currents or altered thermoregulatory mechanisms arising from deposited radiofrequency (RF) energy (14).

MATERIALS AND METHODS

Study Design

Our institution's animal care and use committee approved this study in 21 adult Sprague–Dawley male rats (Charles River Laboratories, Wilmington, Massachusetts) weighing 301–325 g. All rats underwent N1-S1 rat hepatoma cell implantation; each animal was assigned to one of three groups: IO-doped YAS MP injection and AMF exposure, AMF exposure with no particle injection, and control (no injection, AMF, or MR imaging; used only for baseline inductively coupled plasma optical emission spectroscopy [ICP-OES]). Liver and tumor specimens were harvested for histopathologic analysis and ICP-OES measurements for MP detection.

Tumor Implantation

Anesthesia was induced with ketamine (75–100 mg/kg) and xylazine (2–6 mg/kg) administered by intramuscular injection. N1-S1 cells (CRL-1604; American Type Culture Collection, Manassas, Virginia) were maintained in a humidified 5% CO_2 atmosphere at 37°C in Dulbecco modified Eagle medium (Invitrogen, Carlsbad, California) supplemented with 10% fetal bovine serum (Atlanta Biologicals, Lawrenceville, Georgia), 100 U/mL penicillin, and 100 μg/mL streptomycin (Invitrogen). Cells were subcultured every 2–3 days. Cell viability was tested with trypan blue (Mediatech, Herndon, Virginia) staining confirming more than 90% cell viability before implantation. The left lateral lobe of the liver was exposed following a midline subxiphoid incision and minilaparotomy. N1-S1 rat hepatoma cells (6×10^6 cells in 0.2 mL Dulbecco modified Eagle medium) were slowly injected ($\geq$ 30 s) directly under the hepatic capsule. Absorbable hemostatic gauze (LifeScience Plus, Mountain View, California) was applied at the injection site to prevent reflux, and the abdomen was surgically closed in two layers. Tumor growth was allowed for 7–8 days to a desired size of 1.0 cm in diameter (15).

IO-YAS MP Preparation and Phantom Studies

Through an established collaboration with Mo-Sci (Rolla, Missouri), MPs were designed and synthesized specifically for applications in thermoradiotherapy and MR imaging. These MPs were composed of Fe_3O_4 nanocrystals dispersed throughout the YAS glass with approximately 50% IO by mass. The final glass MPs were between 20 and 64 μm in size and had a specific gravity of 3.59 g/cm^3.

To investigate the potential of these magnetic yttrium MPs to generate heat in the presence of an applied AMF, sample concentrations of 72.5, 110, and 145 mg/mL were prepared in 2 mL H_2O. A 2 mL H_2O sample served as the control. Each sample was placed in a glass vial within a cylindrical methacrylate vial carrier (Kimble Cruse,