Evaluation of a tissue-mimicking thermochromic phantom for radiofrequency ablation

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Purpose: This work describes the characterization and evaluation of a tissue-mimicking thermochromic phantom (TMTCP) for direct visualization and quantitative determination of temperatures during radiofrequency ablation (RFA).

Methods: TMTCP material was prepared using polyacrylamide gel and thermochromic ink that permanently changes color from white to magenta when heated. Color vs temperature calibration was generated in MATLAB by extracting RGB color values from digital photographs of phantom standards heated in a water bath at 25–75 °C. RGB and temperature values were plotted prior to curve fitting in MATHEMATICA using logistic functions of form $f(t) = a + b/(1 + e^{(c(t-d))})$, where a , b , c , and d are coefficients and t denotes temperature. To quantify temperatures based on TMTCP color, phantom samples were heated to temperatures blinded to the investigators, and two methods were evaluated: (1) visual comparison of sample color to the calibration series and (2) *in silico* analysis using the inverse of the logistic functions to convert sample photograph RGB values to absolute temperatures. For evaluation of TMTCP performance with RFA, temperatures in phantom samples and in a bovine liver were measured radially from an RF electrode during heating using fiber-optic temperature probes. Heating and cooling rates as well as the area under the temperature vs time curves were compared. Finally, temperature isotherms were generated computationally based on color change in bisected phantoms following RFA and compared to temperature probe measurements.

Results: TMTCP heating resulted in incremental, permanent color changes between 40 and 64 °C. Visual and computational temperature estimation methods were accurate to within 1.4 and 1.9 °C between 48 and 67 °C, respectively. Temperature estimates were most accurate between 52 and 62 °C, resulting in differences from actual temperatures of 0.6 and 1.6 °C for visual and computational methods, respectively. Temperature measurements during RFA using fiber-optic probes matched closely with maximum temperatures predicted by color changes in the TMTCP. Heating rate and cooling rate, as well as the area under the temperature vs time curve were similar for TMTCP and *ex vivo* liver.

Conclusions: The TMTCP formulated for use with RFA can be used to provide quantitative temperature information in mild hyperthermic (40–45 °C), subablative (45–50 °C), and ablative (>50 °C) temperature ranges. Accurate visual or computational estimates of absolute temperatures and ablation zone geometry can be made with high spatial resolution based on TMTCP color. As such, the TMTCP can be used to assess RFA heating characteristics in a controlled, predictable environment. [<http://dx.doi.org/10.1118/1.4953394>]

Key words: tissue-mimicking phantom, thermochromic, thermotherapy, radiofrequency ablation, hyperthermia

1. INTRODUCTION

Thermal ablation of solid tumors is routinely performed as a stand-alone therapy to treat organ-dominant focal malignancies. The goal of these noninvasive or minimally invasive procedures is to heat the tumor above a temperature threshold that is sufficient to impart coagulative necrosis (typically >60 °C).¹ High spatial targeting accuracy of heating is impor-

tant in order to mitigate harm to the surrounding tissues, while ensuring irreversible damage to the entire tumor, or to inform when to perform protective maneuvers such as hydrodissection. Therefore, a comprehensive understanding of device- and modality-dependent dynamic heating characteristics is of utmost importance for safe and effective clinical implementation of both mild hyperthermic (40–45 °C) and ablative thermal therapies (>50 °C).^{2,3}

Phantoms emulate properties of biological tissues that are important determinants of thermal therapy device performance, thereby providing a test environment for device characterization and optimization of therapy protocols without risk to animal or human subjects. In order to visualize thermal lesions in a TMP, various formulations have incorporated bovine serum albumin (BSA) into phantoms to identify temperature elevation due to its transparency near room temperature and opacity following heat-induced coagulation.^{4,5} The coagulation threshold temperature of BSA can be adjusted by altering the pH of the phantom, allowing for delineation of regions heated to threshold temperatures relevant to thermal therapy.^{6,7} However, precise, quantitative, and volumetric measurement of absolute temperatures using conventional TMPs requires numerous precisely placed thermocouples that may affect heating patterns during ablation,⁸ distributed fiber-optic sensing systems,^{9,10} or use of magnetic resonance imaging (MRI) thermometry^{11,12} that is resource- and time-intensive (~\$600–700/h; MRI suite times >1 h),^{13,14} limited in availability, and requires MRI compatible devices.¹⁴

Tissue-mimicking thermochromic phantoms (TMTCPs) are tissue-mimicking materials that possess the ability to change color in response to a change in temperature. The latter property, known as thermochromism, may be achieved by inclusion of liquid crystals, leuco dyes, or permanent color-changing inks in a phantom formulation.^{15–19} Recently, thermochromic phantom materials have been used to identify heating patterns during thermal therapies.^{20,21} For example, Dabagh *et al.* described reusable heat sensitive tissue-mimicking phantoms that change color from transparent blue to colorless upon heating.²² However, the color change threshold of 50 °C is relatively low for thermal ablation and there exists a difference between the onset and ending temperatures of the discoloration process. In addition, the reversible nature of the color change requires rapid analysis in order to record accurate temperatures before color reversal. Finally, this strategy is only suitable for small phantoms due to a loss of transparency, required for observation of color changes, at larger sizes. Heat sensitive coating utilizing thermochromic liquid crystals have also been described for quality assurance (QA) purposes of therapeutic ultrasound.²³ However, the combination of a thin layer of thermochromic material on top of an acoustic absorber is not tissue-mimicking and does not inform on volumetric heating patterns or geographies.

We have previously reported the development of a TMTCP material using a permanent color-changing ink.¹⁹ In this study, our objective was to evaluate the ability of the TMTCP to provide quantitative and absolute measurements of temperature elevation for delineation of mild hyperthermic and thermally ablated volumes produced by radiofrequency ablation (RFA). Visual and computational methods are demonstrated for obtaining absolute temperatures achieved during heating based on visible and permanent color changes in the phantom. These methods are used to quantitatively identify temperature isotherms surrounding the RF electrode following ablation of the TMTCP. Finally, results are compared to RF ablation in an *ex vivo* bovine liver.

2. METHODS

2.A. Preparation of TMTCP

The TMTCP material was prepared as described by Negussie *et al.*¹⁹ using polyacrylamide gel (PAG) and thermochromic ink that permanently and gradually changes color from white to magenta when heated to temperatures between 25 and 75 °C. The phantom formulation, summarized in Table I, was prepared for RFA by adjusting salinity to match that of biological tissues, since this parameter has enhanced influence in RFA. Phantom ingredient ratios were selected based on existing literature,^{4,6,19} as well as on preliminary experiments in which the ink concentration was adjusted to produce good color intensity and gradient. Briefly, an aqueous solution of 40% (w/v) acrylamide/bis-acrylamide (National Diagnostic, Atlanta) with feed ratio of 19:1 (acrylamide to bis-acrylamide) was mixed with degassed, deionized water. Subsequently, sodium chloride (0.9% w/v) (Sigma Aldrich, Milwaukee, WI) and MB Magenta NH 60 °C concentrate (5% v/v), LCR Hallcrest, LLC, Glenview) were added to impart electrical conductivity and thermochromic properties, respectively. Finally, ammonium persulfate (APS, Sigma Aldrich, Milwaukee, WI) was added to initiate polymerization, and N, N, N', N'-tetramethylethylenediamine (TEMED, Sigma Aldrich, Milwaukee, WI) was added as catalyst. The final stirred solution was immediately transferred to a 1 l cylindrical plastic container or poured into 4 ml glass vials, sealed, and kept in a cold room (4 °C) until use.

2.B. Characterization of TMTCP color change

TMTCP color vs temperature calibration was generated by submerging capped vials containing TMTCP material in a water bath in triplicate for 10 min at temperatures between 25 and 75 °C, as measured by calibrated optical temperature probes (diameter = 0.56 mm, Luxtron 3100, LumaSense Technologies, Santa Clara, CA). 10 min was selected as the incubation time as it was determined empirically to be sufficient for the whole phantom to equilibrate with the water bath temperature for all target temperatures (data not shown). The vials were then removed from the water bath and allowed to cool to room temperature.

Vials containing TMTCP material were photographed at a standard color temperature of 5500 K at 1, 7, and 14 days after heating under controlled lighting conditions using a portable photography light box (SANOTO 16 × 12 in. Softbox MK40, Whittier, CA) and a Canon Digital EOS T5 SLR camera. The

TABLE I. TMTCP formulation.

Components	Proportion (%)
Deionized water	76.1 (v/v)
40% acrylamide/bis-acrylamide	17.5 (v/v)
Magenta MB60 °C concentrate	5.0 (v/v)
Sodium chloride (NaCl)	0.9 (w/v)
APS	0.14 (w/v)
TEMED	0.14 (v/v)

photographs were color-corrected using the white background of the photo box as reference prior to extraction of red, green, and blue (RGB) color channel values using a custom script in MATLAB (R2013a, MathWorks, Natick, MA). RGB values were plotted as a function of phantom incubation temperature prior to curve fitting using the NonlinearModelFit[] function in MATHEMATICA (Wolfram, Champaign, IL). The generic form of the equation used in the fits was $f(t) = a + b/(1 + e^{(c(t-d))})$, where a , b , c , and d are coefficients and t is the temperature in °C. Mean RGB values from three calibration experiments were used to make a color swatch representing the color of the phantom at each temperature.

2.C. Estimation of temperature based on TMTCP color change

Eight phantom samples were heated in a water bath to temperatures, blinded from three investigators (no special training, qualifications, or expertise required), between 48 and 67 °C. The investigators then estimated the incubation temperatures by visually comparing the color of the phantom samples to the TMTCP phantom standard calibration series. Temperature estimates were also performed *in silico* using the inverse of the logistic functions to convert sample photograph RGB values to absolute temperatures. The above process was repeated three times in its entirety. The purpose of the computational approach was to provide a semiautomated process by which temperature can be estimated from digital photographs of heated phantoms, e.g., following RFA.

2.D. Effect of thermal dose on TMTCP color change

Capped vials containing phantom material were submerged in a hot water bath at constant temperature for 30, 180, 480, and 780 s. Following incubation, vials containing TMTCP material were removed from the water bath, photographed, and analyzed using a custom MATLAB script to record RGB color intensity values, as described above. This process was repeated at 55, 65, and 75 °C.

2.E. Temperature measurements in TMTCP phantoms and *ex vivo* bovine liver during RFA

A water-cooled radiofrequency electrode (Radionics Cool-tip™, Covidien-Medtronic, Boulder, CO) with 3 cm active tip connected to an RF generator (Radionics RFG-3E) was advanced into the center of a TMTCP phantom ($n = 3$) or *ex vivo* bovine liver ($n = 1$). Four fiber-optic temperature probes (Luxtron/LumaSense Technologies, Santa Clara, CA) with 0.5 mm diameter connected to a fiber-optic temperature sensor (m3300, LumaSense Technologies, Santa Clara, CA) were inserted into the phantom or liver using a 19G introducer needle and a custom 3D printed guide at increments of 0.5 cm from the RF electrode (Fig. 1). The temperature measurements were accurate to within 0.2 °C. The tips of the fiber-optic temperature probes were positioned at a depth of 1 cm above the tip of the electrode. The phantom or liver was placed on a grounding pad coupled by conductive electrode gel (Signagel,

FIG. 1. Schematic representation of RF heating in TMTCP phantom. Optical temperature probes (1, 2, 3, 4) were inserted into the phantom at 0.5 cm radial increments from the electrode (RF). The electrode and grounding pad were attached to the RF generator and the grounding pad was coupled to the phantom using conductive electrode gel. The same configuration was used for ablation of the *ex vivo* liver.

Parker Labs, Inc., Fairfield, NJ) and connected to the RF generator. The generator was operated for 12 min at a fixed current of 1.2 A in the phantom and manually adjusted in the *ex vivo* liver to minimize tissue charring. The electrode and grounding pad location as well as RFA duration were the same for both phantom and liver samples. However, there was a small difference (~30%) in phantom sample volume compared to liver sample volume.

The fiber-optic temperature sensor was connected to a computer, which recorded calibrated temperature measurements every 3 s for all four probes. Phantom experiments were performed in triplicate. Following RFA, the phantoms and liver sample were bisected along the length of the RF electrode and photographed. Temperature isotherms were generated in MATLAB using the temperature vs color data (green channel values only) acquired from phantom samples exposed to known temperatures.

3. RESULTS

3.A. Temperature estimation based on visual assessment of TMTCP color change

Changes in color from white to shades of pink and magenta were visible in phantoms heated to temperatures ≥ 40 °C (Fig. 2).

It was possible to estimate the incubation temperature of phantoms exposed to temperatures blinded from the investigators by comparing sample color changes to a series of phantom “standards” exposed to known temperatures, as depicted in Fig. 2. Temperature estimates based on visual assessments of color change were accurate to within an average of 1.4 °C between 48 and 67 °C (Table II). Estimates were most accurate between 52 and 62 °C, resulting in an average difference of 0.6 °C from the actual heating temperature, and were least accurate below 52 °C and above 62 °C, with an average difference of 2.6 °C. This is to be expected since the greatest apparent color changes occur between 52 and 62 °C (Fig. 2).

FIG. 2. Color of TMTC phantoms one day after heating to temperatures between 25 and 75 °C. Color changes are visible after incubating at temperatures above 40 °C.

3.B. Temperature estimation based on computational assessment of TMTCP color change

RGB color intensities were extracted from photographs and plotted against the exposure temperature of phantoms. In all experiments, the greatest change in color intensity was observed for the green channel across the widest range of temperatures, when compared to red and blue channel intensity changes (Fig. 3), providing the greatest resolution and breadth of temperature measurements. Color changes were highly reproducible as demonstrated by the similarity of the fits and their coefficients (Sec. B in the supplementary material²⁴) and close overlap of the transition regions (determined by finding local minima and maxima of second derivatives of the fitted curves, see Sec. B in the supplementary material²⁴) across three experiments [Fig. 3(A)]. RGB values were measured on days 1, 7, and 14 following heating of TMTCP. The color changes were stable over the course of two weeks [Fig. 3(B)].

A color swatch was generated using the mean RGB values from three phantom heating studies providing reference colors for visual assessment of temperature change in the TMTCP (Fig. 4). A gradual change in color is visible between 40 and 64 °C. At temperatures above 64 °C, no further color change was observed.

Temperature estimates based on the computational assessment are shown in Table III. Compared to blue and red color channel data (data not shown), temperature estimates generated from the green color channel data resulted in the lowest mean difference from the actual phantom incubation temperatures. The mean difference was 1.9 °C for phantoms heated to temperatures between 48 and 67 °C.

Interestingly, the color changes observed in the TMTC phantom seemed to only reflect the maximum temperatures achieved (within a temperature range of 40–64 °C), and appeared largely independent of cumulative thermal dose following incubation at temperatures of 55, 65, and 75 °C for 30, 180, 480, and 780 s (Sec. C in the supplementary material²⁴).

3.C. Heating of TMTCP and *ex vivo* liver by RFA

Application of RF to the TMTCP resulted in visible and well-demarcated color changes around the electrode that were then used to estimate temperature [Fig. 5(A)]. Temperatures were measured at various distances from the RF electrode using optical temperature probes. An ovoid ablation zone (temperatures >55 °C), with major axes of 2.4×4.0 cm (width × length), was measured following computational assessment of temperature based on color change. Relatively sharp

TABLE II. Multiple investigator temperature estimates based on visual assessment of color change in TMTC phantoms. “Difference” refers to the difference between the actual incubation temperature and the temperature estimate.

Actual temperature (°C)	Investigator #1		Investigator #2		Investigator #3		Investigator average	
	Visual estimates (°C)	Difference (°C)	Visual estimates (°C)	Difference (°C)	Visual estimates (°C)	Difference (°C)	Visual estimates (°C)	Difference (°C)
62.0	63.0	1.0	62.0	0.0	62.5	0.5	62.5	0.5
58.0	58.0	0.0	58.0	0.0	58.0	0.0	58.0	0.0
67.0	63.5	3.5	63.0	4.0	63.0	4.0	63.2	3.8
56.0	55.0	1.0	56.0	0.0	53.0	3.0	54.7	1.3
53.0	55.0	2.0	54.0	1.0	54.0	1.0	54.3	1.3
48.0	51.0	3.0	51.0	3.0	52.0	4.0	51.3	3.3
64.0	63.5	0.5	64.0	0.0	63.0	1.0	63.5	0.5
58.0	58.0	0.0	58.0	0.0	58.0	0.0	58.0	0.0
Average difference (52–62 °C)	0.8		0.2		0.9		0.6	
Average difference (<52 °C, >62 °C)	2.3		2.3		3.0		2.6	
Average difference (48–67 °C)	1.4		1.0		1.4		1.4	

FIG. 3. (A) RGB values for temperatures between 25 and 75 °C, and fitted logistic functions. Dotted, medium weighted, and heavy weighted lines indicate data from three separate studies. (B) RGB values for temperatures between 25 and 75 °C with fitted logistic functions at 24 h, 7 days, and 14 days postphantom heating (dotted, medium weighted, and heavy weighted lines, respectively). Black dots indicate bounds for transition regions that constitute the domain of inverse functions. Error bars indicate one standard deviation. “R,” “G,” and “B” refer to fits corresponding to red, green, and blue channels, respectively.

color and temperature gradients were revealed at the ablation periphery [Figs. 5(A) and 5(B)]. Temperature estimates (to a maximum estimate of 61 °C) corresponded closely to temperatures measured by the optical probes at four locations extending radially from the electrode in 0.5 cm increments. RF ablation of an *ex vivo* liver [Fig. 5(C)] resulted in an ablation zone of similar dimensions (based on visual assessment of thermally coagulated tissue) as that of the ablated phantoms (Sec. D in the supplementary material²⁴). Maximum radial temperatures were similar in both phantoms and the *ex vivo* liver. However, temperatures plateaued in the *ex vivo* liver presumably due to charring of the tissue proximal to the electrode [Fig. 5(C)].

The maximum temperatures (mean of three experiments) achieved in the phantom at radial distances of 0.5, 1.0, 1.5, and 2.0 cm as measured by optical temperature probes (Fig. 6) were 85.5, 63.7, 49.7, and 36.7 °C, respectively.

The phantom and the *ex vivo* bovine liver demonstrated similar heating profiles (see Sec. A in the supplementary material²⁴). Heating rates for the first 3 min of RFA at radial increments of 0.5 cm from the RF electrode were: 15.1, 6.8, 3.0,

1.1 °C/min and 16.8, 10.4, 4.5, 1.7 °C/min for phantom and liver samples, respectively. However, heating was limited in the liver with high current, due to rapid spikes in impedance resulting from tissue charring. The applied current was manually adjusted to reduce impedance and tissue charring resulting in a plateau in temperature in the liver.

Following cessation of RFA, cooling rates were 5.72, 3.05, 1.33, and 0.33 °C/min and 4.72, 3.20, 1.39, and 0.37 °C/min for phantom and liver, respectively, at radial increments of 0.5 cm from the RF electrode.

4. DISCUSSION

We have previously developed a polyacrylamide-based TMTC phantom that possesses comparable thermal conductivity, thermal diffusivity, and mass density to human liver tissue.¹⁹ In this study, the phantom material was formulated for RFA by adjusting the electrolyte concentration, color-calibrated with temperature, and used for direct visualization and assessment of RFA thermal lesions. The thermochromic ink incorporated into the phantom matrix produced a color change from white to magenta that could be visualized when heated in the range of ~40–64 °C, with no further appreciable color change above this range. Unlike other TM or TMTC

FIG. 4. Color swatch derived from mean RGB values based on three phantom heating experiments at temperatures between 25 and 75 °C.

TABLE III. Temperature estimates based on TMTC phantom color changes assessed computationally using the inverse function of the fitted logistic function from one experiment based on green color channel data only.

Sample #	Actual temperature (°C)	Temperature estimate (°C)	Difference (°C)
1	62.0	64.8	2.8
2	58.0	57.2	0.8
3	67.0	65.7	1.3
4	56.0	54.9	1.1
5	53.0	55.7	2.7
6	48.0	52.7	4.7
7	64.0	65.0	1.0
8	58.0	57.4	0.6
Mean difference, 52–62 °C			1.6
Mean difference, <52 and >62 °C			2.3
Mean difference, 48–67 °C			1.9

FIG. 5. (A) Photograph of TMTC phantom cross section along the electrode following RF heating. (B) Computationally derived temperature gradients based on color changes in TMTC phantom following RF heating. Representative colors were sampled from the color swatch in Fig. 4. (C) Photograph of the ablated region in *ex vivo* bovine liver following RF heating. In all images, “x” represents the position of the optical temperature probe tips at distances of 0.5, 1.0, 1.5, and 2.0 cm for “1,” “2,” “3,” and “4,” respectively.

phantom formulations, this TMTC phantom can be used to report temperatures that span mild hyperthermic (40–45 °C), subablative (45–50 °C), and ablative (>50 °C) ranges. Color changes in the TMTC phantom occur immediately upon heating and are irreversible and stable, allowing for assessment of achieved temperatures even after cooling or at a later date [see Fig. 3(B)]. Incremental and highly visible changes in color occur as a function of temperature, facilitating accurate temperature estimates by simple visual comparison to a calibration series or color swatch, or by straightforward, semiautomated computational analysis. The incremental nature of the color change also allows for precise quantitative assessment of temperature profiles surrounding the RF electrode and subablative temperatures at the thermal margin [Fig. 5(B)].

The two methods presented for determining temperatures based on color changes in the phantom, i.e., visual and computational approaches, resulted in accurate temperature estimates (<2 °C difference from incubation temperatures). Both methods were most accurate in the range of 52–62 °C when compared to the actual water bath temperatures, as this was the range over which the greatest change in color occurred resulting in maximum temperature resolution. Visual estimates were generally slightly more accurate than computational estimates

presumably due to limitations in the accuracy of extracting color intensities from digital photographs due to slight changes in lighting or reflections. However, computational temperature estimates or models may be refined over a wider range by using data from all color channels in the analysis and/or applying other functions such as high order polynomials or piecewise functions that may more closely fit the data. In addition, RGB values may be more accurately measured using spectrophotometric devices.

The TMTC phantom was used to evaluate the geometry and volume of the heated region as well as temperatures following RFA. Temperature isotherms surrounding the RF electrode were calculated by converting green color intensities in the heated region to temperatures [Fig. 5(B)]. Temperature gradients in the heated region were clearly identifiable and revealed a relatively sharp decrease in temperature at the ablation margin. In addition, the color change in the phantom allowed for direct visualization of the ovoid geometry of the heated region when phantoms were bisected. Both the geometry and dimensions of the heated region were similar to the ablated zone in *ex vivo* liver (Sec. D in the supplementary material²⁴).

Irreversible color changes in the phantom, which represent the maximum temperatures achieved during heating,

FIG. 6. Temperature–time profiles in (A) TMTC phantom ($n = 3$) and (B) *ex vivo* bovine liver ($n = 1$) at various distances from the RF electrode. The RF generator was shut off after 12 min of heating and temperature measurements were recorded for 20 min from the beginning of heating. In (A), dotted lines represent one standard deviation of the mean. In (A) and (B) the temperature–time line profiles from top to bottom correspond to measurements at 0.5, 1.0, 1.5, and 2.0 cm distances from the RF electrode, respectively.

corresponded closely with maximum temperatures measured at the same locations using the fiber-optic temperature probes implanted in the phantom. The only exception was at a distance of 0.5 cm from the electrode where differences in temperatures above 63 °C cannot be resolved based on color (i.e., color change of the ink is complete). However, thermochromic inks that possess different color change properties, e.g., lower or higher color change thresholds, or color changes over a wider range of temperatures, may be used. In addition, a thermochromic phantom may be manufactured with two or more different thermochromic inks in order to report on a wider range and/or multiple distinct ranges of temperatures.

Currently, *ex vivo* tissues are commonly used for assessing the treated volume resulting from thermal ablation. However, accessibility to fresh *ex vivo* tissues may be limited and they are often heterogeneous leading to difficulties in interpreting results. Precise placement of thermocouples or fiber-optic thermometers is also difficult and may result in variability in temperature measurements. By contrast, the TMTC phantom described in this work has the capacity to provide volumetric, quantitative temperature information with very high spatial resolution in a controlled, homogeneous environment.

The rate of heating during RFA of the TMTC phantom was similar to that of *ex vivo* liver prior to the onset of tissue charring and corresponding increase in impedance (necessitating a reduction in applied current). Moreover, the cooling profiles following cessation of RFA were very similar for both the phantom and liver, indicating closely matched thermal properties, in agreement with results shown in a previous study.¹⁹

The TMTCP may find use in a variety of applications including characterization of medical imaging systems and in device development, quality assurance, and training. Other potential applications include benchmarking existing and novel RFA systems, as well as evaluation and calibration of noninvasive or minimally invasive sensing technologies such as fiber-optic distributed sensors or computed tomography-, ultrasound, or MRI-based thermometry methods. Importantly, the properties of the phantom can be tailored to mimic different tissues as well as adjusted to meet the requirements of different ablation modalities. For example, the speed of sound and acoustic attenuation of the TMTC phantom material can be modified by, e.g., adding silica particles, propanol, BSA, evaporated milk, and/or corn syrup, for use with HITU applications.^{6,25,26} Similarly, TMTCP properties can be modified to facilitate characterization of laser, RF, and microwave ablations.

Several limitations should be noted. First, the electrical properties of TMTCP were not directly measured in this study. However, they are assumed to be similar to other polyacrylamide phantoms with electrical properties modified by adding, e.g., NaCl, measured over a range of RF frequencies, and found to be comparable to human soft tissues.^{4,27,28} Moreover, comparable thermal and electrical properties of the phantom to those of bovine liver may be inferred based on the similarity of respective heating and cooling profiles. Second, as is the case with most phantoms, temperature measurements may not predict temperatures achieved *in vivo* due to convective heat loss via tissue perfusion and other biological factors that influence

heat transport. This may be partly remedied by embedding a vascular flow network in the phantom²⁹ or by mathematical modeling using *in vivo* perfusion values and temperature input parameters measured empirically in the phantom.³⁰ Third, tissue charring and insulating vaporization, which may occur at very high temperatures near the electrode during RFA, is not well replicated in the phantom. Finally, some bioeffects that are important to thermal therapies result from cumulative thermal dose, i.e., the bioeffects are affected by both the magnitude and the duration of heating.³¹ The heating duration is particularly important for mild hyperthermia applications,³² while bioeffects such as thermal coagulation occur nearly instantaneously at higher temperatures (>56 °C).^{1,33} The color changes observed in the TMTC phantom reflect the maximum temperature achieved (within a temperature range of 40–64 °C) but are mostly independent of cumulative thermal dose (Sec. C in the supplementary material²⁴).

5. CONCLUSION

The phantom provides a measure of absolute temperatures and ablation zone geometry with high spatial resolution within the range of 40–67 °C. Accurate estimations of achieved temperatures in the phantom are possible by simple visual or semiautomated computational methods following RFA. As such, the phantom could be used to assess device- and parameter-specific heating characteristics in mild hyperthermic, subablative, and ablative temperature ranges.

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CONFLICT OF INTEREST DISCLOSURE

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¹ B. J. Wood, J. R. Ramkaransingh, T. Fojo, M. M. Walther, and S. K. Libutti, "Percutaneous tumor ablation with radiofrequency," *Cancer* **94**, 443–451 (2002).

² K. F. Chu and D. E. Dupuy, "Thermal ablation of tumours: Biological mechanisms and advances in therapy," *Nat. Rev. Cancer* **14**, 199–208 (2014).

³ D. F. Saldanha, V. L. Khiatani, T. C. Carrillo, F. Y. Yap, J. T. Bui, M. G. Knuttinen, C. A. Owens, and R. C. Gaba, "Current tumor ablation technologies: Basic science and device review," *Semin. Interventional Radiol.* **27**, 247–254 (2010).

⁴ Z. Bu-Lin, H. Bing, K. Sheng-Li, Y. Huang, W. Rong, and L. Jia, "A polyacrylamide gel phantom for radiofrequency ablation," *Int. J. Hyperthermia* **24**, 568–576 (2008).

- ⁵M. J. Choi, S. R. Guntur, K. I. Lee, D. G. Paeng, and A. Coleman, "A tissue mimicking polyacrylamide hydrogel phantom for visualizing thermal lesions generated by high intensity focused ultrasound," *Ultrasound Med. Biol.* **39**, 439–448 (2013).
- ⁶M. McDonald, S. Lochhead, R. Chopra, and M. J. Bronskill, "Multi-modality tissue-mimicking phantom for thermal therapy," *Phys. Med. Biol.* **49**, 2767–2778 (2004).
- ⁷P. N. Brodin, A. Partanen, P. Asp, C. A. Branch, C. Guha, and W. A. Tomé, "A simple method for determining the coagulation threshold temperature of transparent tissue-mimicking thermal therapy gel phantoms: Validated by resonance imaging thermometry," *Med Phys.* **43**, 1167–1174 (2016).
- ⁸D. A. Christensen, "Thermal dosimetry and temperature measurements," *Cancer Res.* **39**, 2325–2327 (1979).
- ⁹D. Tosi, E. G. Macchi, and A. Cigada, "Fiber-optic temperature and pressure sensors applied to radiofrequency thermal ablation in liver phantom: Methodology and experimental measurements," *J. Sensors* **2015**, 1–22.
- ¹⁰D. Tosi, S. Poeggel, G. Leen, E. Lewis, E. G. Macchi, G. Braschi, M. Gallati, A. Cigada, and S. Rossi, *Presented at the Proceedings of IEEE Sensors* (2014).
- ¹¹B. D. de Senneville, C. Mougenot, B. Quesson, I. Dragonu, N. Grenier, and C. T. W. Moonen, "MR thermometry for monitoring tumor ablation," *Eur. Radiol.* **17**, 2401–2410 (2007).
- ¹²A. S. Mikhail, A. Partanen, P. Yarmolenko, A. M. Venkatesan, and B. J. Wood, "Magnetic resonance-guided drug delivery," *Magn. Reson. Imaging Clin. North Am.* **23**, 643–655 (2015).
- ¹³M. Petrou, B. R. Foerster, and D. S. Reich, "Translational research in radiology. Challenges and role in a patient-based practice," *Acad. Radiol.* **16**, 593–596 (2009).
- ¹⁴A. H. Mahnken, A. Buecker, E. Spuentrup, G. A. Krombach, D. Henzler, R. W. Günther, and J. Tacke, "MR-Guided radiofrequency ablation of hepatic malignancies at 1.5 T: Initial results," *J. Magn. Reson. Imaging* **19**, 342–348 (2004).
- ¹⁵O. Panák, M. Držková, and M. Kaplanová, "Insight into the evaluation of colour changes of leuco dye based thermochromic systems as a function of temperature," *Dyes Pigm.* **120**, 279–287 (2015).
- ¹⁶V. U. Kakade, G. D. Lock, M. Wilson, J. M. Owen, and J. E. Mayhew, "Accurate heat transfer measurements using thermochromic liquid crystal. Part 1: Calibration and characteristics of crystals," *Int. J. Heat Fluid Flow* **30**, 939–949 (2009).
- ¹⁷V. U. Kakade, G. D. Lock, M. Wilson, J. M. Owen, and J. E. Mayhew, "Accurate heat transfer measurements using thermochromic liquid crystal. Part 2: Application to a rotating disc," *Int. J. Heat Fluid Flow* **30**, 950–959 (2009).
- ¹⁸P. J. Newton, J. Paul, Y. Yan, N. E. Stevens, S. T. Evatt, G. D. Lock, and J. M. Owen, "Transient heat transfer measurements using thermochromic liquid crystal. Part 1: An improved technique," *Int. J. Heat Fluid Flow* **24**, 14–22 (2003).
- ¹⁹A. H. Negussie, A. Partanen, A. S. Mikhail, S. Xu, N. Abi-Jaoudeh, S. Maruvada, and B. J. Wood, "Thermochromic tissue-mimicking phantom for optimisation of thermal tumour ablation," *Int. J. Hyperthermia* **32**, 239–243 (2016).
- ²⁰A. Dabbagh, B. J. Abdullah, C. Ramasindarum, and N. H. Abu Kasim, "Tissue-mimicking gel phantoms for thermal therapy studies," *Ultrason. Imaging* **36**, 291–316 (2014).
- ²¹I. Butterworth, J. Barrie, B. Zeqiri, G. Zauhar, and B. Parisot, "Exploiting thermochromic materials for the rapid quality assurance of physiotherapy ultrasound treatment heads," *Ultrasound Med. Biol.* **38**, 767–776 (2012).
- ²²A. Dabbagh, B. J. J. Abdullah, N. H. Abu Kasim, and C. Ramasindarum, "Reusable heat-sensitive phantom for precise estimation of thermal profile in hyperthermia application," *Int. J. Hyperthermia* **30**, 66–74 (2014).
- ²³F. Qureshi, Z. Larrabee, C. Roth, A. Hananel, M. Eames, D. Moore, J. Snell, N. Kassell, and J.-F. Aubry, "Thermochromic phantom for therapeutic ultrasound daily quality assurance," *J. Ther. Ultrasound* **3**(Suppl 1), P72 (2015).
- ²⁴See supplementary material at <http://dx.doi.org/10.1118/1.4953394> for quantitative characterization of heating curves, thermal dose, and ablated zone dimensions, as well as for coefficients of logistic functions.
- ²⁵E. L. Madsen, G. R. Frank, and F. Dong, "Liquid or solid ultrasonically tissue-mimicking materials with very low scatter," *Ultrasound Med. Biol.* **24**, 535–542 (1998).
- ²⁶A. Partanen, C. Mougenot, and T. Vaara, "Feasibility of agar-silica phantoms in quality assurance of MRgHIFU," *AIP Conf. Proc.* **1113**, 296–300 (2009).
- ²⁷A. Surowiec, P. N. Shrivastava, M. Astrahan, and Z. Petrovich, "Utilization of a multilayer polyacrylamide phantom for evaluation of hyperthermia applicators," *Int. J. Hyperthermia* **8**, 795–807 (1992).
- ²⁸I. Dos Santos, D. Correia, A. J. M. Soares, J. A. Góes, A. F. Da Rocha, D. Schutt, and D. Haemmerich, "A surgical device for radiofrequency ablation of large liver tumors," *Physiol. Meas.* **29**, N59–N70 (2008).
- ²⁹R. Greaby, V. Zderic, and S. Vaezy, "Pulsatile flow phantom for ultrasound image-guided HIFU treatment of vascular injuries," *Ultrasound Med. Biol.* **33**, 1269–1276 (2007).
- ³⁰A. Gasselhuber, M. R. Dreher, A. Partanen, P. S. Yarmolenko, D. Woods, B. J. Wood, and D. Haemmerich, "Targeted drug delivery by high intensity focused ultrasound mediated hyperthermia combined with temperature-sensitive liposomes: Computational modelling and preliminary *in vivo* validation," *Int. J. Hyperthermia* **28**, 337–348 (2012).
- ³¹S. A. Sapareto and W. C. Dewey, "Thermal dose determination in cancer therapy," *Int. J. Radiat. Oncol., Biol., Phys.* **10**, 787–800 (1984).
- ³²A. Partanen, M. Tillander, P. S. Yarmolenko, B. J. Wood, M. R. Dreher, and M. O. Köhler, "Reduction of peak acoustic pressure and shaping of heated region by use of multifoci sonications in MR-guided high-intensity focused ultrasound mediated mild hyperthermia," *Med. Phys.* **40**, 013301 (13pp.) (2013).
- ³³W. C. Dewey, "Arrhenius relationships from the molecule and cell to the clinic," *Int. J. Hyperthermia* **10**, 457–483 (1994).