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Experimental and numerical investigation of heat confinement during nanoparticle-assisted thermal therapy☆

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ABSTRACT

Nanoparticle-assisted thermal ablation therapy has recently evolved as a promising future therapy for cancer treatment. This therapy is advantageous because it is potentially much more selective than traditional methods (surgery or chemotherapy) in terms of destroying cancerous cells while leaving healthy tissue intact. In this study, heat confinement and thus the healthy tissue sparing characteristics, were experimentally investigated. Two Agarose gel samples of cylindrical shape were synthesized for evaluating the heat confinement in the axial and radial directions. A specified region of the gel was embedded with gold nanoparticles which were synthesized in this study (mimicking an injection of nanoparticles to the tumor region), while the rest of the plain gel mimics the surrounding healthy tissue. These Agarose gel samples were irradiated through fiber optic and the spatiotemporal temperature response was measured. A numerical model was also developed and validated against these experiments. The measurements were then extended to real tumor-tissue by taking into account blood perfusion and metabolic heat generation. It is observed that with the proposed approach, heat can be well confined to the nanoparticle embedded region. This study shows that with a well-designed system it is possible to obtain thermal ablation of the tumor region while sparing healthy tissue 3 mm beyond the tumor boundary.

1. Introduction

Thermal therapy involves the use of heating or cooling to treat a variety of diseases. For cancer treatment, thermal therapy in the form of thermal ablation has extensive potential [1–3]. Thermal ablation involves heating a tissue to a temperature of 50–60 °C which destroys the targeted cells. The advent of nanotechnology has served to enhance the efficacy of thermal ablation therapy, particularly with regard to tumor specific confinement of the therapy [4–6]. In this approach, a tumor is embedded with nanoparticles and is irradiated with a light source which matches the plasmon response of nanoparticles — preferably within the 'therapeutic window' (600 nm–1300 nm). Here, nanoparticles act as heat sources (through irradiation absorption) and the therapeutic parameters can be designed to confine the heat within a specific region. Generally, tumors are surrounded by healthy tissue, so selectivity (especially in the vicinity of critical organs) throughout the therapy is extremely important.

There are few published studies [4,5,7–10] which provide spatial temperature details and what is available does not comprehensively address the heat confinement characteristics. Numerical studies by the co-authors [11] and others [12,13] have shown that it is possible to achieve thermal ablation temperatures in a specific region through proper selection of parameters (irradiation intensity & duration, optical coefficients and concentration of the nanoparticles). However, experimental validation of this has not yet been demonstrated, although it represents a critical factor in deciding whether such therapy is preferable to traditional methods in practice.

As such, this study experimentally evaluates the spatiotemporal extents of heat confinement and thus the sparing characteristics of healthy tissue surrounding a representative tumor. Two Agarose tissue phantoms were synthesized to evaluate the radial and axial confinement of heat within nanoparticle embedded regions. The gold nanoparticles that were embedded within the Agarose gel, were also synthesized and characterized in this study. The irradiation intensity, duration, beam diameter and volume fraction were selected based on our earlier numerical study [11] which reported the ideal parameters needed to achieve the desired thermal ablation temperature in the tumor region. A two-dimensional numerical model was developed and validated through temperature measurements of Agarose gel. This model was extended to account for the blood perfusion and metabolism present in

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real tissue. Finally, the attained temperatures (within and in the vicinity of a tumor) were experimentally measured for gel and extended to the real tissue, while achieving thermal ablation of the tumor region. Ultimately, the aim for this therapy is to attain thermal ablation temperatures within the tumor region, but to have these fall to within safe limits immediately adjacent to the tumor-healthy tissue boundary.

2. Material and methods

2.1. Synthesis and characterization of gold nanoparticles

Gold nanoparticles were synthesized, in water, using the seed mediated chemical method [14]. In this method, sodium borohydride is used as a reducing agent and cetyltrimethylammonium bromide (CTAB) is used as a capping agent to stabilize the gold nanoparticles. The elemental form of gold was verified using XRD measurements. The plasmon response (optical absorption spectrum) of these nanoparticles was measured using a spectrophotometer (Carry 5000 UV–VIS–IR, Varian) and is shown in Fig. 1(a). The spectral characteristics of radiation are shown in Fig. 1(b). The mean nanoparticle diameter (intensity based) was measured with a dynamic light scattering instrument (Zetasizer Nano ZS90, Malvern Instruments), and was found to be 51 nm. Thus, a nominal size of 50 nm was used in the calculations.

The concentration of gold in the solution was estimated to be 97 μg/ml. The concentration value is in agreement with the values reported in the literature [4,5]. Through the diameter of gold nanoparticles and the amount of nanofluid used to make the gel, the volume fractions of the nanoparticles was calculated to be 0.0005%. Since the volume of Agarose was much less than that of the base nanofluid, the same concentration was assumed in the gel phantom. The considered value of volume fraction is based on average diameter of nanoparticles, but there is unavoidable variation of nanoparticle size within the sample. The synthesized nanoparticles were centrifuged to remove them from the chemical precursors. So, the resulting nanoparticle concentration was higher in the final solution and this volume fraction was 0.002%. Fig. 1(a) shows the measured plasmon response for the nanoparticles used in this study. It is seen from Fig. 1(a) that the plasmon response is similar to that reported in the published studies [15,16].

2.2. Experimental setup for evaluating the heat confinement

A cylindrical 0.5% Agarose gel phantom was synthesized (0.5 g Agarose powder in 100 ml of water), with a diameter of 12 mm and length 20 mm. Agarose gel has been used as tissue mimic in earlier studies involving thermal therapies [17,18]. It is to be noted that many different biological characteristics exist between tumor tissues and surrounding tissues — blood perfusion rates, pH, oxygen levels, metabolism, etc. From a thermal therapy point of view, the blood perfusion and metabolism (metabolic heat) are relevant. As we know that the gel phantoms do not possess blood perfusion and metabolic phenomenon, the main purpose of using gel phantom (in the present study) is to experimentally measure/quantify the heat generation phenomenon. Comparing our experimental results with the well-established Pennes' bioheat model (Section 3.3), we can gain insight into how these parameters control the potential effectiveness of the treatment. Fig. 2(a) shows the experimental setup used for evaluating heat confinement in the axial direction and thus inferring the axial healthy tissue sparing characteristics. In the present study, an upper region of the gel was embedded with gold nanoparticles, which represents a 4 mm thick tumor region having a uniform distribution of gold nanoparticles. The uniform distribution of nanoparticles was visually checked through the uniform spatial purple color (dark top region) of the gel. The other 16 mm thick surrounding region is plain gel, which was prepared by dissolving the Agarose in water. Depending on the delivery method, the nanoparticle distribution within a tumor may vary and thus influence the thermal ablation temperatures [19,20].

Similarly, Fig. 2(b) shows the gel sample for evaluating the radial extent of heat confinement. In this sample, Agarose gel was prepared in a cylindrical geometry with a diameter of 40 mm and a depth of 4 mm. The central region (diameter 12 mm) of the gel was embedded with gold nanoparticles while the surrounding region is plain gel (without nanoparticles). The gel phantom was prepared to avoid any air gap between the nanoparticle region and plain region. Firstly the nanoparticle gel was prepared and then liquid plain gel was poured around it. So, the final gel was cross-linked on solidification. Also, there was not any noticeable melting of Agarose gel during the experiments. The dimensions of the nanoparticle embedded region of the gel were of the order of typical skin tumors [21,22]. The gel phantoms were irradiated through an optical fiber bundle and the temperature rise was recorded at various axial and radial locations using fine gauge (wire diameter 75 μm) k-type thermocouples (3971589, RS make) located within the gel, as shown by red–yellow wires in Fig. 2. The temperature data was acquired from the thermocouples using a 16 channel data acquisition module (NI 9214, National Instruments). This module has built in cold junction temperature compensation and provides isothermal connections for temperature measurements with sensitivity of 0.02 °C.

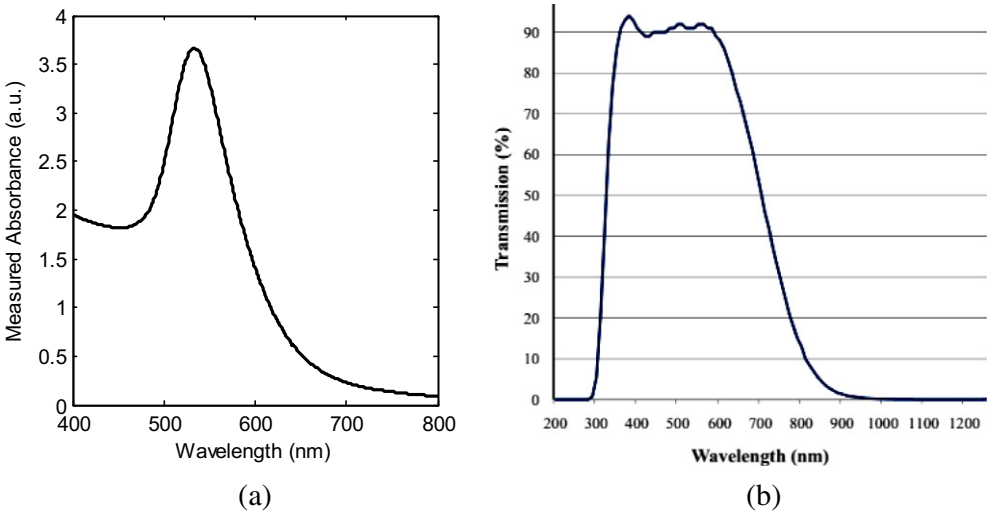

Fig. 1. (a) Measured optical absorption spectra of synthesized gold nanoparticles. Absorption peaks at 530 nm. Measurement was done using a spectrophotometer (Carry 5000, Varian). (b) Spectral transmittance of the glass coating and hence irradiation (obtained from the supplier).