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Effect of tumor properties on energy absorption, temperature mapping, and thermal dose in 13.56-MHz radiofrequency hyperthermia

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ABSTRACT

Computational techniques can enhance personalized hyperthermia-treatment planning by calculating tissue energy absorption and temperature distribution. This study determined the effect of tumor properties on energy absorption, temperature mapping, and thermal dose distribution in mild radiofrequency hyperthermia using a mouse xenograft model. We used a capacitive-heating radiofrequency hyperthermia system with an operating frequency of 13.56 MHz for in vivo mouse experiments and performed simulations on a computed tomography mouse model. Additionally, we measured the dielectric properties of the tumors and considered temperature dependence for thermal properties, metabolic heat generation, and perfusion. Our results showed that dielectric property variations were more dominant than thermal properties and other parameters, and that the measured dielectric properties provided improved temperature-mapping results relative to the property values taken from previous study. Furthermore, consideration of temperature dependency in the bio heat-transfer model allowed elucidation of precise thermal-dose calculations. These results suggested that this method might contribute to effective thermoradiotherapy planning in clinics.

1. Introduction

Mild hyperthermia (39–44 °C) is a complimentary therapeutic technique used in conjunction with radiation and chemotherapy to enhance therapeutic effectiveness (van der Zee, 2002). To integrate the use of hyperthermia therapy in clinics, hyperthermia-treatment planning tools are used to optimize cancer-treatment quality with the help of computational simulations. Generation of a computational model, calculation of power deposition, and determination of temperature distribution and thermal dosing are the major steps in hyperthermia-treatment planning (Paulides et al., 2013). Additionally, the dielectric properties of tissues should be carefully identified to allow accurate energy and thermal dose calculations. Several studies reported the dielectric properties of normal tissues over a wide range of frequencies (Gabriel et al., 1996a, 1996b, 1996c); however, additional studies are needed to understand the behavior of tumor properties, especially at frequency ranges < 50 MHz.

In hyperthermia-treatment planning using electromagnetic fields, dielectric property values are vital for the calculation of specific absorption rates (SAR) and thermal doses. The energy absorption of biological tissues in electromagnetic fields depends upon their relative permittivity (dielectric constant) and electrical conductivity with respect to a specific frequency (Joines et al., 1994). With increases in frequency, the relative permittivity and conductivity are expected to change by maintaining the same trend from low to high frequencies (Gabriel et al., 1996a, 1996b, 1996c). For frequencies < 100 MHz, increases in the dielectric properties of tumor tissues results from the charging of cell membranes, with minor contributions from protein constituents and ionic diffusion along the tissue surface (Foster and Schepps, 1981). For frequencies > 100 MHz, the dielectric properties of tissues can be explained based on the percentage of water content in the tissues, with tumors speculated to have higher water content than the surrounding normal tissues (Foster and Schepps, 1981; Joines et al., 1994). In general, tumors exhibit relatively high electrical conductivity and relative permittivity as compared with normal tissues; however, previous studies reported that some tumors exhibit similar or lower conductivity and permittivity values as compared with normal tissues (Joines et al., 1994; Yoo, 2004).

Unlike normal tissues, conductivity and permittivity values in tumors differ and are subject to change according to the organ or tissues in which they grow (Yoo, 2004). A previous study reported that for frequencies ranging from 50 MHz to 100 GHz, the permittivity and

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conductivity of malignant tissues in organs, such as bladder, colon, liver, lymph nodes, mammary glands, spleen, and testis, were higher than that in normal tissues; however, few tumors, such as those in the kidney and lung, showed lower permittivity than the normal tissues, and the lung tumor showed lower conductivity relative to the normal tissues (Joines et al., 1994). Few studies have measured the dielectric properties of tumors using mouse models (Raoof et al., 2013; Rogers et al., 1983; Yoo, 2004). One group measured properties associated with brain, gastric, breast, and colon tumors from 500 MHz to 5 GHz, reporting that all tumors exhibited relatively high dielectric properties as compared with normal tissues; however, each of those tumor-specific dielectric properties was similar (Yoo, 2004). A study of normal tissues, liver, and pancreatic tumors reported that tumors exhibited higher dielectric properties than normal liver and pancreas tissue. Additionally, they reported that the values for the liver tumors were higher than those of pancreatic tumors within a frequency range of 10 MHz to 3 GHz (Raoof et al., 2013). Moreover, liver-tumor measurements from 100 MHz to 5 GHz in four cancer patients showed that tumors in each patient displayed a different dielectric property, with one patient having relatively low permittivity values relative to normal liver tissues due to pathological changes (Peyman et al., 2015). Variations in dielectric properties were also reported in colorectal cancer tissues at different tumor stages across a frequency range of 50–500 MHz (Li et al., 2017).

In addition to frequency specific dielectric properties, temperature dependence associated with thermal properties, metabolic heat generation, and perfusion should also be considered while determining temperature distribution and thermal dose. Most previous studies did not consider variations in properties for simulations of mild and ablative hyperthermia-temperature ranges (Kok et al., 2017, 2014; Oh et al., 2014; Zastrow et al., 2010; Zorbas and Samaras, 2014). A previous study showed that optimal dielectric and thermal-property values can partially neglect the effect of perfusion in hyperthermia-treatment planning (Ahmed et al., 2008). Other studies on temperature dependence in biological tissues showed that thermal properties are dependent on temperature (Bhattacharya and Mahajan, 2003; Choi et al., 2013). Additionally, consideration of variations in metabolic heat generation and blood perfusion is a better predictor of accurate heat transfer in tissues than using normothermic values associated with these properties (Rai and Rai, 1999). Therefore, accurate calculation of the thermal dose for numerical simulations requires determination of the effects of thermal properties, perfusion, and metabolic heat generation. Few hyperthermia studies with tissue mimicking phantoms showed good temperature mapping in experiments and simulations using measured dielectric properties of normal and tumor phantoms (Kim and Lee, 2015; Oh et al., 2014).

Previously, we reported temperature measurements using a phantom model and patient-specific simulations in real human-anatomy models to demonstrate selective heating characteristics and electrode optimization of treatment planning (Hossain et al., 2016; Prasad et al., 2016). In the present study, the effect of tumor properties on calculating energy absorbance and thermal dose was determined based on dielectric property measurement and temperature-dependent thermal properties, perfusion, and metabolic heat generation.

2. Materials and methods

2.1. Measurement of dielectric properties

The dielectric property measurement involves the measurement of complex permittivity, which consists of relative permittivity and imaginary permittivity and can be defined as follows:

$$\varepsilon^*(\omega) = \varepsilon'(\omega) - j\varepsilon''(\omega) \tag{1}$$

where $\varepsilon^*(\omega)$ is the complex permittivity, ω is the angular frequency, $\varepsilon'(\omega)$ is the relative permittivity or dielectric constant, $\varepsilon''(\omega)$ is the imaginary permittivity or dielectric loss factor. Imaginary permittivity can be converted into effective conductivity as follows:

$$\sigma = \omega\varepsilon_0\varepsilon'' \tag{2}$$

where σ is the conductivity, and ε_0 is the permittivity of free space.

According to a previously reported procedure (Raoof et al., 2013), fresh tumor samples (2 cm) excised sharply from mice were used for the measurements, which were performed using an Agilent 85070E high-temperature coaxial dielectric probe connected to an Agilent E4991A impedance analyzer, with a manufacturer uncertainty of 5% (Agilent Technologies, Santa Clara, CA, USA) (Raoof et al., 2013) across the frequency range 10–1000 MHz. Repeated measurements were performed for accuracy, and theoretical fitting of the measurement was accomplished using the dielectric dispersive-fitting tool available in Sim4Life software (https://www.zurichmedtech.com/sim4life/), with an accurate fitting achieved using a multi-pole Lorentz model (Banks et al., 2008; Stoykov et al., 2003; Sullivan, 1992).

$$\varepsilon^*(\omega) = \varepsilon_\infty + \sum_{p=1}^{P} \frac{a_p \Delta\varepsilon \omega_p^2}{\omega_p^2 + 2j\omega\delta_p - \omega^2} + \frac{\sigma}{j\omega\varepsilon_0} \tag{3}$$

where ε_∞ is the infinity permittivity, $\Delta\varepsilon$ is the difference between static and infinity permittivity, ω_p is the angular frequency of pole, a_p is the amplitude of pole, δ_p is the damping frequency of pole and, σ is the electric conductivity.

2.2. In vivo mouse experiments

Experiments were performed on a human tumor xenograft model. The local ethical committee for animal experiments approved the experimental protocol used in this study (17–0110-S1A1). Cancer cells (squamous cell carcinoma of the lung) were injected into the femoral region and allowed to grow until reaching 200 mm^3. A radiofrequency (RF) capacitive-heating device (LAB EHY 100; Oncotherm, Budapest, Hungary) with an operating frequency of 13.56 MHz was used for the experiments (Kim et al., 2018). Fiber optic temperature sensors were inserted into the tumor and surrounding tissues to estimate temperature increases and output power during RF heating. The experimental scheme involving the RF generator, electrode, data-acquisition temperature measurement, and sedating system is shown in Fig. 1(a). Initially, the mouse was kept in a chamber with circulating isoflurane gas for sedation, followed by transfer to a position above the heating system. To keep the mouse sedated throughout the experiment, isoflurane gas mixed with oxygen was administered through an inhaler. Four fiber optic sensors were placed 1) inside the tumor (5 mm from the electrode), 2) in nearby tissue (2 mm from the tumor), 3) in the rectum, and 4) toward the middle of the mouse at the interface between mouse and bed [Fig. 1(b)]. The positions of the sensors were chosen at the center region of the tumor to ensure heat transfers through the tumor, at the closest possible surrounding tissue to attain the temperature of tissue near the tumor, in the rectum to obtain variations in core body temperature, and at the interface between bed and skin to maintain body heat during experiment. Measurements were recorded using a data-acquisition system connected to a computer. The response time of the sensors was 9 s for sensor 1, 20 s for sensor 2, 67 s for sensor 3, and 81 s for sensor 4. Electrodes used for RF heating were placed on the tumor region and subjected to water cooling [Fig. 1(c)]. A total of four tumor-induced mice were used for the experiments, with each mouse treated four times over a 2-week period. The tumor was heated to 42 °C and maintained at that temperature for 30 min to establish a heating protocol.

2.3. Numerical simulation

Numerical simulations comprised a combination of electromagnetic and thermal simulations. All simulations were performed using the