Original Article

Physical Parameters Measurement of Breast Equivalent Phantom for Clinical Studies in Radiofrequency Hyperthermia

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Radio Frequency Ablation.

Abstract

Purpose: Breast cancer is one of the fatal diseases which causes death in women. Microwave hyperthermia is one way to treat cancer cells by irradiating RF waves to the cells and increasing their temperature. In our study, we fabricated breast phantom. Then we placed it in an RF field with a frequency of 13.56 MHz. We measured the temperature difference in several parts of the phantom, eventually.

Materials and Methods: We designed a 5cm radius hemisphere geometry which is similar to real breast considering as fat tissue, glandular tissue as a semi-oval embedded in the hemisphere and a 1cm radius sphere as a tumor region in it. Then, it is utilized in a three-dimensional printer. After that, each layer of the phantom was filled with a suitable mixture of oil-gelatin which had similar properties of a real breast. Finally, we placed it in a microwave device with a frequency of 13.56 MHz.

Results: During exposing RF to the phantom, the temperature differences were measured in four different points of the phantom. Our power and time in this treatment were 40 watt and 5 minutes, respectively. Temperature and Specific Absorption Rate (SAR) plots were obtained in several graphs for 5 minutes.

Conclusion: The results showed that the heat generation with this frequency is much enough to cause damage in tumor tissues while healthy tissues tolerate a lower amount of heat. The results have shown that this band of frequency can cause ablation in tumor tissues and can be used for breast cancer treatments.

1. Introduction

Breast Cancer is the most frequent malignancy and the leading cause of death in women worldwide [1]. Despite progressive achievements in clinical treatment, in the majority of the breast cancer patient's treatment failure still occurs and women continue to die, mainly due to an evolutionary process toward a metastatic and treatment-resistant disease [16-18].

Hyperthermia therapy, or the application of supra-normal body temperatures as an adjunct treatment for cancer, has been studied for decades due to the relatively high thermal sensitivity of malignant cells compared to healthy tissue [5,6]. Heat can be delivered by a variety of techniques such as radio frequency, microwave radiation, regional perfusion therapy, laser ablation or magnetic hyperthermia [12-14]. Radiofrequency ablation has reached an importance position in recent years for the treatment of cancerous tumors. Hyperthermia is mostly identified by a range of temperatures from 40 to 48°C or similar maintained at a treated site for one hour or more [19–22]. This amount of increase in temperature can cause damage in tumor cells while normal tissue can tolerate it.

In hyperthermia, two different kinds of properties are important and should be considered: dielectric and thermal properties. Several researchers have reported breast phantoms for hyperthermia. In 2005, Lazebnik *et al.* used the oil-gelatin mixture to provide homogenous

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breast phantom in 0.5-20 GHz. However, in their investigation, dielectric properties are just emulated and the geometry that they designed had no similarity to the real breast [9]. In 2012, Stang *et al.* investigated prototype systems in breast cancer treatment. In their investigation, the dielectric properties of breast were just considered and the thermal properties were neglected [2]. Yuan *et al.* considered both dielectric and thermal properties of breast tissues in 100-433 MHz frequency. However, they did not use suitable geometry for breast [3]. In 2013, Miaskowski *et al*. investigated by considering both properties in 150KHz, but they did not use suitable geometry either [4]. In 2015, Nguyen *et al.* fabricated a phantom with dielectric and thermal properties in the GHz band of frequency. Although they used proper geometry, they did not use it in experimental studies [10]. In 2017, Tayel *et al.* worked on a grid antenna array for breast cancer treatments. In their investigation, both kinds of properties were considered, but they did not consider gland tissue of the breast. In 2019, Mukherjee *et al*. studied the time reversal method in the hyperthermia of breast cancer. In their simulation, only dielectric properties were calculated. Most of the earlier studies investigated in frequency ranges that were not used in clinical treatments of breast cancer and they did not use a clinical device as RF source.

According to researches [7], the frequency is inversely proportional to the depth of penetration. In 900 MHz, we can reach 4.2 cm depth of body and frequencies above this amount cannot be used for breast tumors in clinical treatments.

In this paper, we designed a suitable geometry for breast and fabricated a phantom with an oil-gelatin mixture which has similar thermal and dielectric properties to a real breast. After measuring properties of the phantom, we put this phantom in an electromagnetic field with a frequency of 13.56 MHz. Our main purpose of this investigation is to work in a frequency band which is used in a clinical device and clinical treatments. The frequency between 10-15 MHz is a suitable range in clinical therapies. In this band, the penetration depth is well enough to cover the whole body and this band can cause ablation in tumor cells with the least damage to healthy tissues.

2. Materials and Methods

We divided this section into five parts: designing geometry, fabricating phantom, thermal and dielectric properties measurement, disposing phantom in RF radiation, and Specific Absorption Rate (SAR) measurement. Each part is explained as extremely as below:

2.1. Designing Geometry

In this part, we designed a proper geometry in the solid software (Solidworks 2018 SP5) which represented the real breast. We considered three different tissues of a cancerous breast: fat, gland, and tumor tissues. A 5cm radius hemisphere was designed as a whole breast, which was a 3.5×5cm diameter semi-oval embedded in it. This semi-oval represented the gland tissue and the distance between hemisphere and semi-oval represented the fat tissue. In the bottom of this semi-oval, there was a 1cm radius sphere as a tumor. We utilized this geometry with a 3D printer, eventually. Figure 1 shows the design and fabricated phantom.

2.2. Fabricating Phantom

The properties of the oil-gelatin phantom are much similar to real tissues compared to other materials [11]. For instance, agar mixtures have a high melting point (approximately 80˚C). Hence, they can preserve their shape. However, their permittivity is lower than the real tissues. Therefore, they cannot represent the dielectric properties of tissues [15]. TX-150 can successfully provide for high water content tissues such as the tumor, but it cannot be used for low water content tissues like a fat [11]. However, the oil-gelatin mixture can be easily prepared homogeneously and by adding formaldehyde, their shape maintains in high temperature. Hence, their behavior in an electromagnetic field in hyperthermia can represent real tissues much more than other materials.

Our main materials for fabricating phantom were calfskin gelatin (Sigma), safflower oil, and water. Adding NaCl to the mixture helped us to adjust electrical conductivity (σ) for tumor tissue. The specific heat capacity of oil is lower than water (specific heat capacity of oil is about 1.64 $({}^{j}/{}_{kgo_C})$ while it is 4.42 $({}^{j}/{}_{kgo_C})$

for water). Therefore, for adjusting these properties in the tissues which had high specific heat capacities like tumor and gland, we used water instead of oil.

Because we had both hydrophilic and hydrophobic materials in our mixture, we used SLS (Sodium Lauryl Sulfate) as a surfactant to bring homogeneity in our phantom. For making phantom stable at high temperature, we added formaldehyde to the mixture to increase the melting point of the phantom and prevent it from transfiguration. The weight values of materials for each tissue are shown in Table 1.

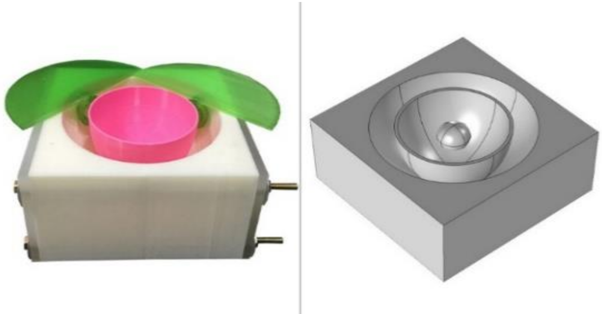

Figure 1. The design of phantom and the 3D-printed shape of the phantom

Table 1. Weight of each material in each tissue

Tissue (gr) / Material	Fat	Gland	Tumor
Oil	121.49	24.68	1
Gelatin	13.69	32.81	1.9
Water	35.93	98.74	5.7
Salt	0	0	0.18
Surfactant	6.8	1.38	0.07
Formaldehyde	2.16	1.73	0.11

For fabricating this phantom, the fat mixture was made initially and filled in a region of the phantom which was prepared as a fat layer. According to Lazebnik *et al.*, we stayed at least 5 days since formaldehyde cross-linking of gelatin to be completed [9]. Then, the gland mixture was made and again after 5 days, we divided phantom into two parts to put tumor at it. For making tumor completely sphere with a radius of 1cm, we used a cube which had a spherical hole with a radius of 1 cm in it (Figure 2.). The final phantom after fabricating is shown in Figure 3.

Figure 2. The cube for fabricating tumor tissue. There is a hole on it to inject the mixture in it

Figure 3. Oil-gelatin phantom of the breast

2.3. Thermal and Dielectric Properties Measurement

After fabricating phantom, in this part, we measured the thermal and the dielectric properties of phantom and compared it with real breast tissues.

For measuring thermal properties (specific heat capacity, thermal conductivity, and density), nine samples were taken from different parts of each tissue to improve measurement accuracy and their amount was measured by a calorimeter. The thermal properties are shown in Table 2.

Generally, the dielectric properties include relative permittivity and conductivity. The permittivity is described as a complex physical quantity which contains a real part and an imaginary part. The real part is defined as the ability of a medium to store electric field energy and the imaginary part is defined as a loss factor which describes the dissipated energy in the material. The complex permittivity is expressed as follow:

$$\varepsilon = \varepsilon' - j\varepsilon'' \quad (1)$$

Where ε , ε' and ε'' are the complex permittivity, the real part of the permittivity and the imaginary part of the permittivity (loss factor), respectively.

The permittivity calculations in the complex form had lots of difficulties. Hence, we used some simplifications and capacitor concepts. According to the capacitor equations, the capacity amount of capacitor in the air to medium describes the complex permittivity and normalized permittivity of tissues according to vacuum represents relative permittivity. Equations 2 and 3 show the relative permittivity and the conductivity relations:

$$\varepsilon_r = \frac{C}{K} \quad (2)$$

$$\sigma = \frac{G\varepsilon_0}{K} \quad (3)$$

Where C, K, ε_0 and G are the capacitance of the capacitor in tissue, the capacitance of the capacitor in the air, the permittivity of free space, and the conductivity of the capacitor, respectively. Table 3 shows the dielectric properties of the phantom.

Table 2. The values of thermal properties in each tissue of phantom with the real values of breast tissues

Tissues		Fat	Gland	Tumor
Specific Heat Capacity	Real amount	2280	3639	3639
$(^{j}/_{kgo_C})$	Measure amount	2300	3670.5	3670.5
Thermal Conductivity	Real amount	0.3	0.56	0.56
$(^{w}/_{mo_C})$	Measure amount	0.3	0.56	0.56
Density	Real amount	1069	1050	1050
$(kg\ /\ m^3)$	Measure amount	1070	1048	1048

Table 3. The values of dielectric properties in each tissue of the phantom

Tissues	Fat	Gland	Tumor
Relative Permittivity ε_r	11.8	138.4	142.5
Electrical Conductivity $\sigma(s.m^{-1})$	0.03	0.63	0.71

2.4. Disposing Phantom in the RF Radiation

After properties measurement, we disposed it in an RF field. Our device was Celsius TCS (Celsius42+ GmbH, Cologne, Germany) with a frequency of 13.56 MHz (Figure 5-a). This device had two pair electrode in two different sizes (15 and 25 cm) (Figure 5-b) which are located on the top and at the bottom of the phantom. The shape of the electromagnetic field between the two electrodes is shown in Figure 4.

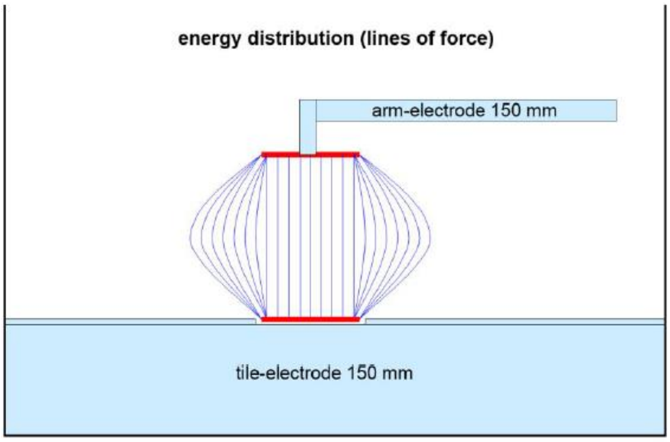

Figure 4. Energy distribution (lines of force); 150 mm electrode on the top, 150 mm electrode on the bottom

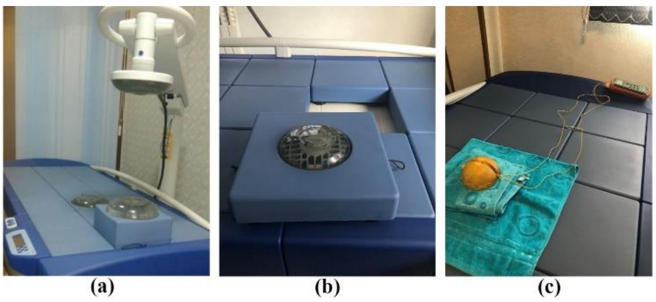

Figure 5. (a): Celsius TCS (Celsius42+ GmbH, Cologne, Germany). **(b):** The bottom electrode (150 mm) of the device. **(c):** Phantom on hyperthermia device. The phantom is shifted up to adjust the tumor on the focus point

2.5. Specific Absorption Rate (SAR) Measurement

Specific Absorption Rate (SAR) is the rate at which the human body tissue absorbs energy when applying an external force. This external force is energy generated by an electric field, electromagnetic waves or ultrasound

waves. In this study, SAR is the amount of heat generated by the electromagnetic waves measured in W/m^3 [8].
Since the only heat source and heat absorber were electromagnetic field and phantom, respectively, SAR was considered to be heat generator The SAR at several points of the phantom was calculated as:

$$SAR(w/m^3) = \rho c \frac{dT}{dt}\Big|_{t=0} \qquad (4)$$

3. Results

When we use the same size electrode at each side, focusing occurs in the center point and we have a maximum intensity at this point. Hence, we adjusted the tumor in this point to prevent healthy tissue from extra heating, particularly fat (because of low specific heat capacity). Figure 5-c shows the phantom between two electrodes.

The temperature measurement of some specific point of the phantom is achieved by a thermocouple (Extech421509). Mean value of the temperature after 5 times for each tissue is plotted in Figure 6. We tested several powers and time with both sizes of electrodes to find proper parameters. After multiple tests, we noticed that the proper power and time for the breast in this frequency is 40Watt and 5minutes, respectively. As a matter of fact, in this power and time, the temperature of the tumor from the center to the border of it was about 3-3.6 ˚C, while this amount for gland and fat was 1.8 and 1.6 ˚C, respectively. As shown in Figure 7., at the early time of treatment, the temperature from center to the border of the tumor was approximately close to each other. However, by increasing the time, heat transfer from the center to the border decreased and the temperature difference of these two points increased. With the help of Equation (4), we calculated SAR of all tissues and obtained the amount of energy that absorbed in each tissue during treatment. The amounts of SAR for each tissue are shown in Figures 8-10. Moreover, the total SAR of the phantom is plotted in Figure 11.

As shown in the figures, the specific absorption rate (SAR) of the tumor is extremely high at the beginning and it approximately decreased over time and become steady. Moreover, the total Specific Absorption Rate (SAR) in the phantom was inversely proportional to the radius due to the tissues properties and focusing. The high conductivity of the tumor caused a high specific absorption rate and consequently increased the heat generation in this region.

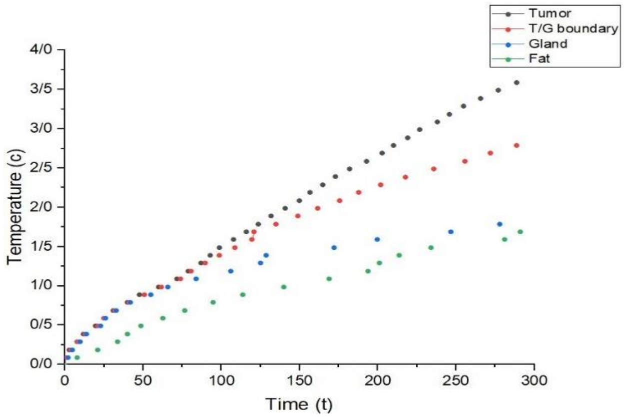

Figure 6. Increasing of temperature in several points of the phantom (T/G boundary point is the boundary between tumor and gland tissues)

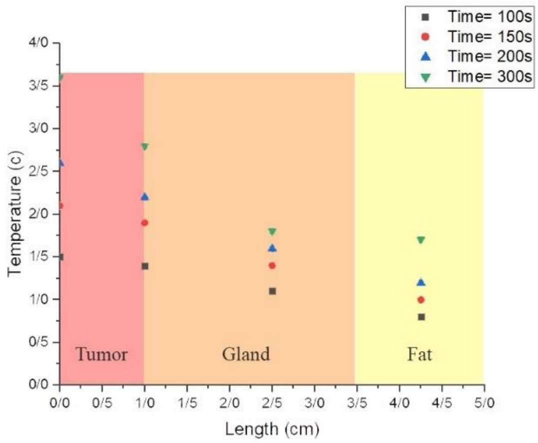

Figure 7. Temperature amounts for each tissue in four different times

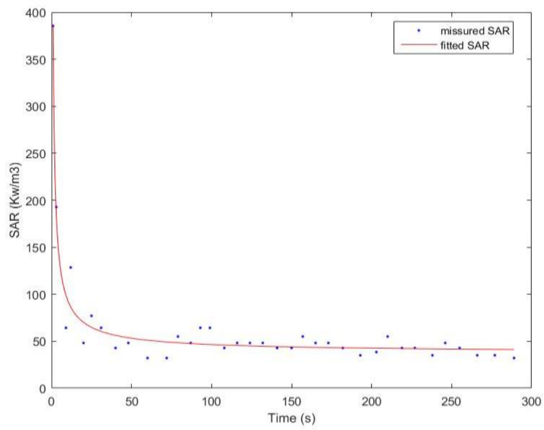

Figure 8. The SAR distribution on the tumor for 5 minutes

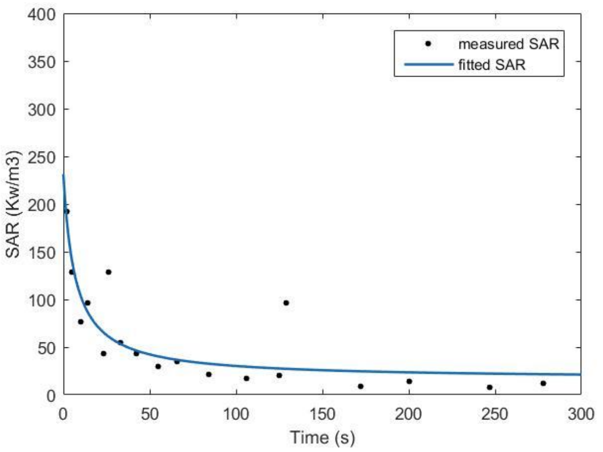

Figure 9. The total Specific Absorption Rate (SAR) distribution on the gland for 5 minutes

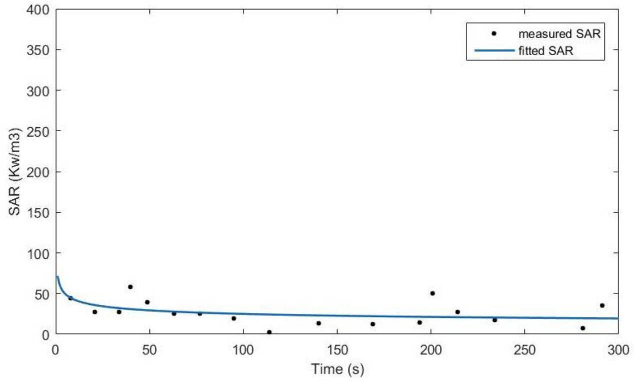

Figure 10. The total Specific Absorption Rate (SAR) distribution on the fat for 5 minutes

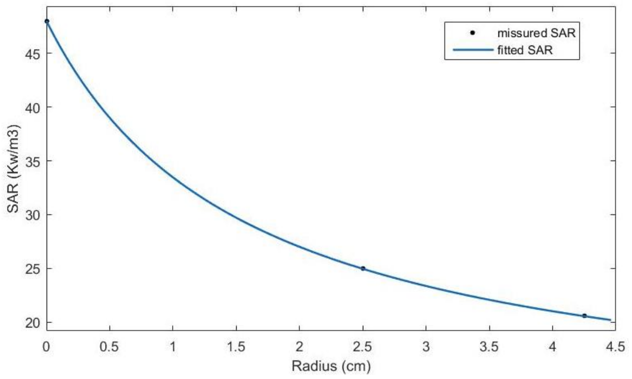

Figure 11. The total Specific Absorption Rate (SAR) distribution on the phantom for 5 minutes

4. Discussion

We fabricated a homogenous breast phantom for radio-frequency hyperthermia studies in 13.56 MHz. This frequency is used for clinical treatment. In earlier researches, only mimicking phantom was important. In most studies, they used frequency bands that were not used in clinical treatments and their RF sources were not clinical devices. We studied the proper mixture which had more similarity to the real breast than other mixtures. After measuring important parameters and making sure that this phantom could represent real cancerous breast well, we placed it in the electromagnetic field that had clinical application in cancer treatment. Because breast tissue contains fat and the specific heat capacity of fat is lower than other parts, it is so important to have an exact focus point and use power and time that preserve this tissue from damage. By measuring the temperature increasing at different points and calculating the specific absorption rate, we reached a huge achievement in ablation breast cancerous tissues with this frequency and device. The behavior of this phantom in 13.56 MHz radio-frequency hyperthermia device showed extreme temperature increasing in tumor tissue without causing damage in healthy tissues. For further studies, we suggest using nanoparticles in the tumor region to provide more heat generation in this part with the same power and time.

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