

ORIGINAL ARTICLE

Numerical Modeling of Locoregional Hyperthermia in Human Pelvic Cancers Applied with Capacitive System: Experimental and Simulation Study

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Abstract

Purpose: This study aimed to estimate the rate of temperature rise during the radiofrequency capacitive heating (13.56 MHz, 300 watts) to defined geometries including 6 simple geometric models, a virtual phantom, and a real section of the human pelvis obtained by CT-scan. The importance of this study is in the process of Hyperthermia Treatment Planning (HTP).

Materials and Methods: In this research, COMSOL software has been used to numerical model and simulate the three-dimensional (3D). First, six models with simple cylindrical geometry were developed to simulate the Radiofrequency (RF) capacitive hyperthermia treatment sessions. The diameter of the capacitor plates used was 25 cm, which was placed on a layer of water. To perform hyperthermia treatment planning with real geometry based on CT images, the pelvic area was downloaded from the slicer software and the generated mesh was transferred to COMSOL. Finally, a virtual phantom was used to validate the simulation, which means that the results of this simulation have been confirmed by experimental studies in the literature.

Results: The findings of this study indicated that capacitive hyperthermia is an effective deep treatment method especially for lean patients, so that for all models, an increase in temperature to a depth of 12 cm was observed. The thermometric data obtained from the simulation method showed a good agreement with the results obtained from the clinical and tissue equivalent phantom thermometry. The results showed that the simulation can predict temperature changes during capacitive hyperthermia for lean patients with greater accuracy than obese patients.

Conclusion: The results of comparing temperature profiles of the models taken from the platform provided with the experimental studies, showed relatively good simulation accuracy, that can be used to develop software for capacitive heating treatment planning.

Keywords: Locoregional Hyperthermia; Capacitive Hyperthermia; Finite Element Method; Numerical Modeling; COMSOL Multiphysics.

1. Introduction

Hyperthermia, as a non-invasive mechanism of local heating of the tumor up to 41–45 °C, maintaining this temperature for 1 hour, has proven to be a potent adjuvant therapy for chemotherapy and radiotherapy [1–3]. Superficial hyperthermia is applied to tumors infiltrating up to a depth of 4 cm in the tissue. Recurrent and metastatic melanoma and recurrent breast cancer are examples of superficial tumor sites where the effectiveness of combined radiotherapy and hyperthermia in a clinical trial has been demonstrated [4]. Studies have shown that when hyperthermia was added to radiation therapy, the overall response to recurrent breast cancer increased from 41% to 59%. For malignant tumors, a two-year calculated local tumor control rate of 28% has been reported for radiotherapy alone, increasing to days 46 plus hyperthermia. These studies highlight the importance of shedding hyperthermia in cancer treatment modalities [5, 6]. In order to improve the outcomes of cancer treatment, according to the reports of clinical studies, considering the existing challenges, the development of new combination therapies for cancer therapy will be very helpful, among these potent adjuvant treatments is non-invasive radiofrequency hyperthermia [7, 8]. The most important challenge in hyperthermia is how to non-invasively measure the deep tissue temperature and the lack of transparency in the temperature distribution in the tissue [9, 10]. Especially for the treatment of RF capacitive hyperthermia or coil due to the mechanism of heat production, the use of appropriate deep thermometry methods is very important [11–13]. Surface temperature can be determined with conventional thermometry methods such as IR cameras, but deep temperatures are complex, and simulation studies can largely remove this ambiguity [9, 14]. Due to the differences and research gaps in this field, we can refer to the recent study of Kok *et al.*, who examined different methods of applying radiofrequency exposure, each of which had advantages and disadvantages [15]. The results of their simulations, which used the developed Plan2Heat hyperthermia treatment planning software based on voxel-based finite difference calculations, compared with the clinical results showed that therapeutic temperatures for capacitive hyperthermia in patients with deep-seated pelvic tumors can be predicted with

high accuracy [15, 16]. Various studies have confirmed that treatment by hyperthermia processes offers a favorable result, however, there is still controversy [17–19]. Due to a lack of enough data in the field of locoregional hyperthermia with capacitive heating, in this study, our aim is to simulate capacitive heating based on various models with COMSOL multiphysics software [20].

2. Materials and Methods

2.1. Design of Research Strategy

For this purpose, studies have been conducted in three steps: a) Defining the parameters of capacitive heating systems; b) phantom design; c) simulation

2.2. Capacitive Heating Systems

In this study, we used some models that are used to investigate possible situations in the design of hyperthermia treatment with a capacitor consisting of two electrodes. For capacitive heating systems, the size of the electrodes was 25 cm in diameter. The two electrodes were the same size and the operating frequency was 13.56 MHz. The device voltages were applied with a power of 150 watts. For capacitive heating, two electrodes were placed above and bottom of the patient's limbs. Locoregional hyperthermia for pelvic tumor locations was applied: cervix, prostate, bladder, and rectum. Small fatless, and large patient models were derived from standard clinical CT data sets. IR cameras and thermocouples were used during the treatment to monitor the temperature for simulation.

2.3. Simulation for the Phantom Study

The material between the two electrodes is equivalent to body tissue, which acts as a dielectric and is heated by the application of voltage. These voltages are applied with a power of 150 watts. For simulation, we use the COMSOL software environment to create the simple geometry. For this purpose, the body is first made of a cylinder with an oval base, which for a fat person has a large diameter of 40 cm and a small diameter of 22.5 cm, and for a thin person its large diameter is 30 cm and its small diameter is 20 cm. Two discs with a diameter of 25 cm

were used to simulate capacitive electrodes. In the next step, to perform finite element simulation, the geometry created in the previous section was meshed into interconnected components called free tetrahedral meshes, with a maximum mesh element size of 2.2 cm and a minimum mesh size of 0.44. The most important step in performing hyperthermia simulation is to make a mesh based on defined geometry. If the number of meshes created is not optimal or their number is not enough, the simulation will encounter an error. Therefore, the type of mesh we want to perform for simulation is the free tetrahedral type. In order to obtain the temperature profile in one section of the model made for the two groups of obese and lean samples, the geometries defined below have been used, so that a point starts from the bottom and ends at the top of the model's abdomen. Figure 1 shows the simple geometries in detail.

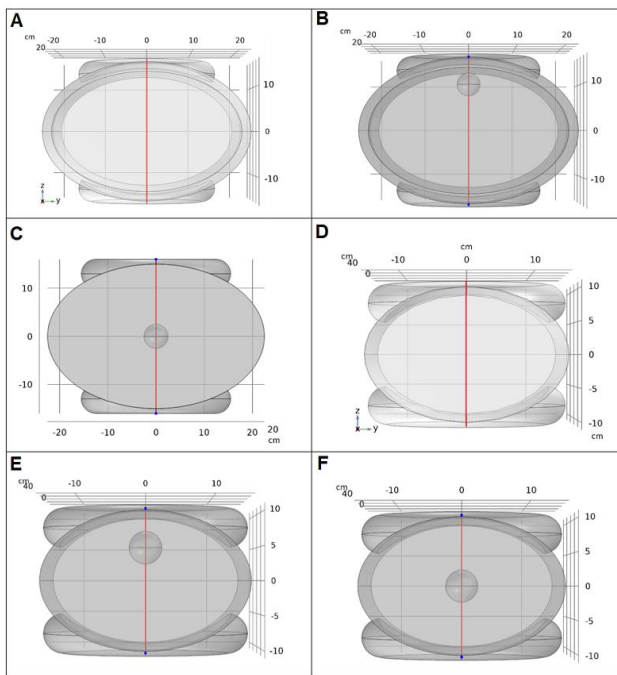


Figure 1. Different geometries based on the location of the hypothetical tumor as well as the extent of obesity and thinness. The red line indicates the temperature measurement path along the red line from bottom to top

2.4. Simulation for Human Model

Patient simulations were performed through structural CT scan images, that are taken from the abdomen of a patient treated with RF hyperthermia. Figure 2A is related to the axial view of a patient's

pelvic/abdomen region obtained from the slicer software [21]. It is obtained by combining the following shapes of 2-dimensional geometry. Using the open-source slicer software, we entered the captured images into the software, and by introducing the intensity threshold on the Hounsfield unit, we determined the different parts of the tissue, including muscle, fat, and skin, and took a 3-dimensional output in STL image format (Figure 2B). In the last step, we selected a section of the CT images that includes the hypothetical part of the individual tumor, and entered it into COMSOL software, and by entering the physical parameters (Table 1) such as tissue density, tissue conduction, etc., we performed the simulation in COMSOL software and obtained the necessary outputs (Figure 2C). This output included time curves in terms of temperature and heat distribution generated in the real physical model.

2.5. Treatment Planning and Theoretical Model

To model the hyperthermia process, we entered input parameters including the power of the radiotherapy device, the frequency of the radiator (usually a constant value), electrical conductivity, and the density of tumor and healthy tissue including; fat, muscle, and bone. Using the RF modules and the bi-density distribution of power density, we obtained the temperature distribution with the RF module of COMSOL software [22], which is designed based on solving Maxwell equations. The radiofrequency module of COMSOL software uses low equations, including the Maxwell equations and the last equation which ends in the Laplace Equations 1-6:

$$\nabla \times E = -\frac{\partial B}{\partial t} \text{ and } \nabla \cdot E = 0 \quad (1)$$

$$\nabla \times H = j + \frac{\partial D}{\partial t} ; \nabla \cdot D = \rho \quad (2)$$

$$\nabla \cdot [\sigma(-\nabla V) + j\omega\epsilon(-\nabla V)] = 0 \quad (3)$$

$$\sigma_e = \sigma + \omega\epsilon'' \quad (4)$$

$$\epsilon = \epsilon' - j\epsilon'' \quad (5)$$

$$\nabla \cdot [-(\sigma + \omega\epsilon'' + j\omega\epsilon')\nabla V] = 0 \quad (6)$$

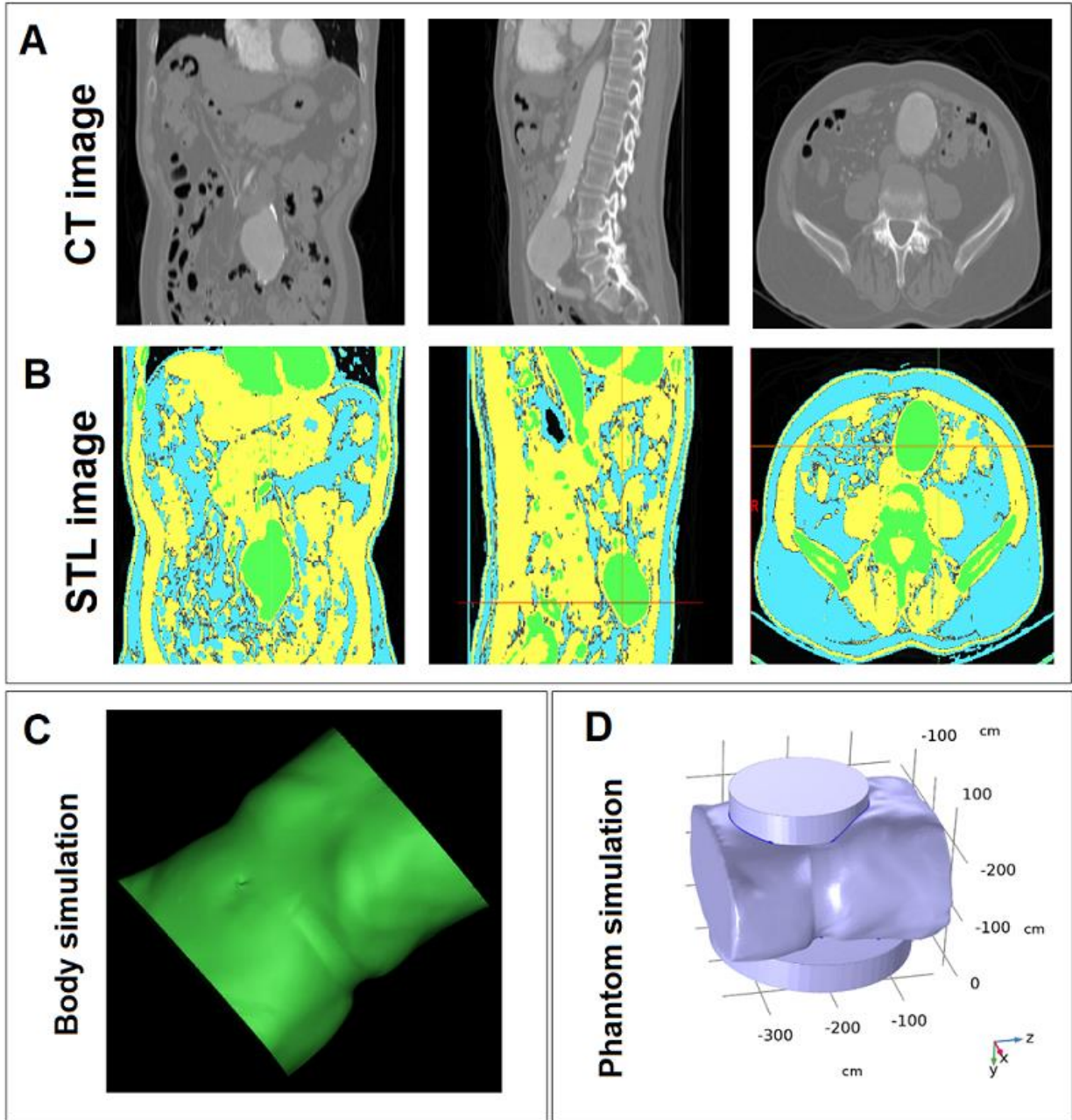


Figure 2. A) Human abdomen/pelvis CT images (coronal, sagittal, axial), B) Reconstruction of STL format images by introducing Hounsfield unit by slicer software, C) Simulation of body images by introducing physical parameters by COMSOL software, D) Simulation of human phantom by COMSOL software

After determining the QRF parameter using the RF module with the heat transfer of heat pliers, the temperature distribution created by the radiation of RF waves to the tissue was obtained by [23]:

$$\rho c \frac{\partial T(x, y, z, t)}{\partial t} = \nabla(k \nabla(r, t)) + Q_b + Q_m + Q_{RF} \quad (7)$$

with ρ (the density, c the specific heat capacity of the tissue), T (the temperature in all three dimensions of the coordinate system), t (the time), (k the thermal conductivity), Q_b (the effect of heat due to blood perfusion), Q_m (metabolic heat), and finally, the last parameter (Q_{RF}) represents heat from actions.

2.6. Validation

By comparing the simulation results with the experimental studies of Sahinbas *et al.*, we used a

Table 1. List of Parameters With Numerical Values and Their Units Used for Simulation

Parameters	Tumor	Water	Muscle	Bone	Air	Fat
Density [kg/m ³]	1090	1000	1090	1908	1.29	911
Specific heat capacity [J/kgK]	3421	4180	3421	1313	1000	2348
Thermal conductivity [W/m°C]	0.49	6.0	0.49	0.32	0.024	0.21
Volumetric perfusion rate [kg.m ⁻³ s ⁻¹]	1.8	-	3.6	0.12	-	1.1
Conductivity [S/m]	0.63	9.4e-5	0.63	0.05	0	0.03
Relative permittivity [-]	87.7	138.4	138.4	30.6	1	11.8

phantom that met the conditions applied in the simulation [6]. Accordingly, if the simulation results were correct, it would be expected that the temperature obtained by the simulation would correspond to the temperature measured by the thermometer (Figure 3).

3. Results

3.1. Phantom Simulations

Figure 4 (A-F) shows the heating of an equivalent phantom for an obese and lean individual in tumor-free, superficial tumors (tumor with a diameter of 3 cm), and deep-seated tumors with capacitive electrodes located at the top and bottom of the phantom. For a fair comparison between the top and bottom electrodes, both electrodes were 25 cm in diameter. The maximum temperature in the phantom was 43 degrees. In smaller samples, the temperature distribution was more uniform. The simulation results

showed better heating for superficial tumors that were close to the electrodes. By increasing the distance from the electrodes to deep tumors, especially for obese specimens, the heat distribution was somewhat reduced. Figure 5 (A & B) shows the thermal distribution map of the phantom when it has been in the capacitor for 20 minutes. In this figure, the thermal data obtained from the simulation and measurement of heat by thermocouples are shown for the points near the electrodes with a red line and for the central points of the phantom with a blue line. A comparison of the results shows a high correlation between the simulation data and the experimental data.

3.2. Human Results

In this part, in order to upgrade the previous simple models and obtain accurate and reliable temperature distribution, CT scan images were used. CT scans will show the patient's body geometry and the location of the tumor. As mentioned, in the previous geometric

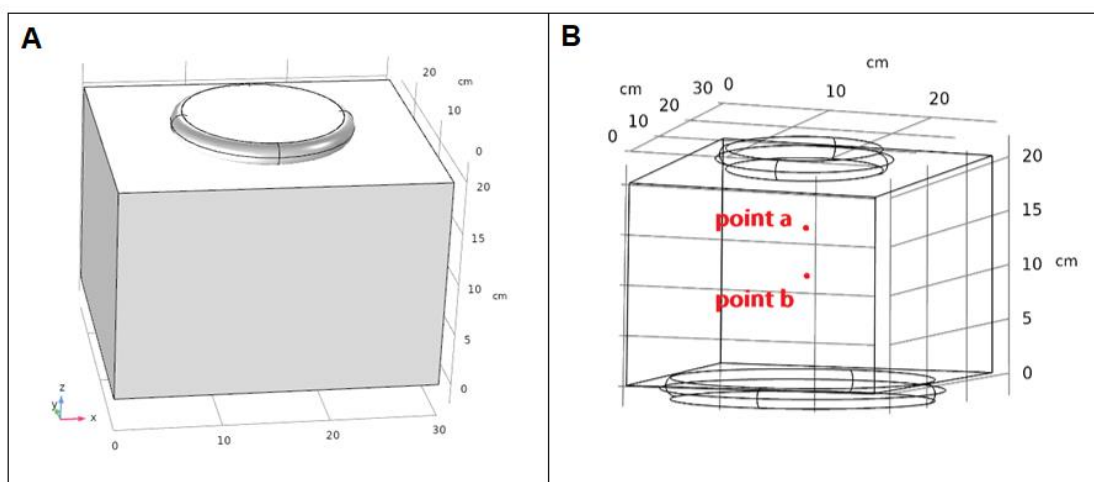


Figure 3. A) simulated model of experimental phantom, B) Position of measuring points at 5 and 10 cm, respectively

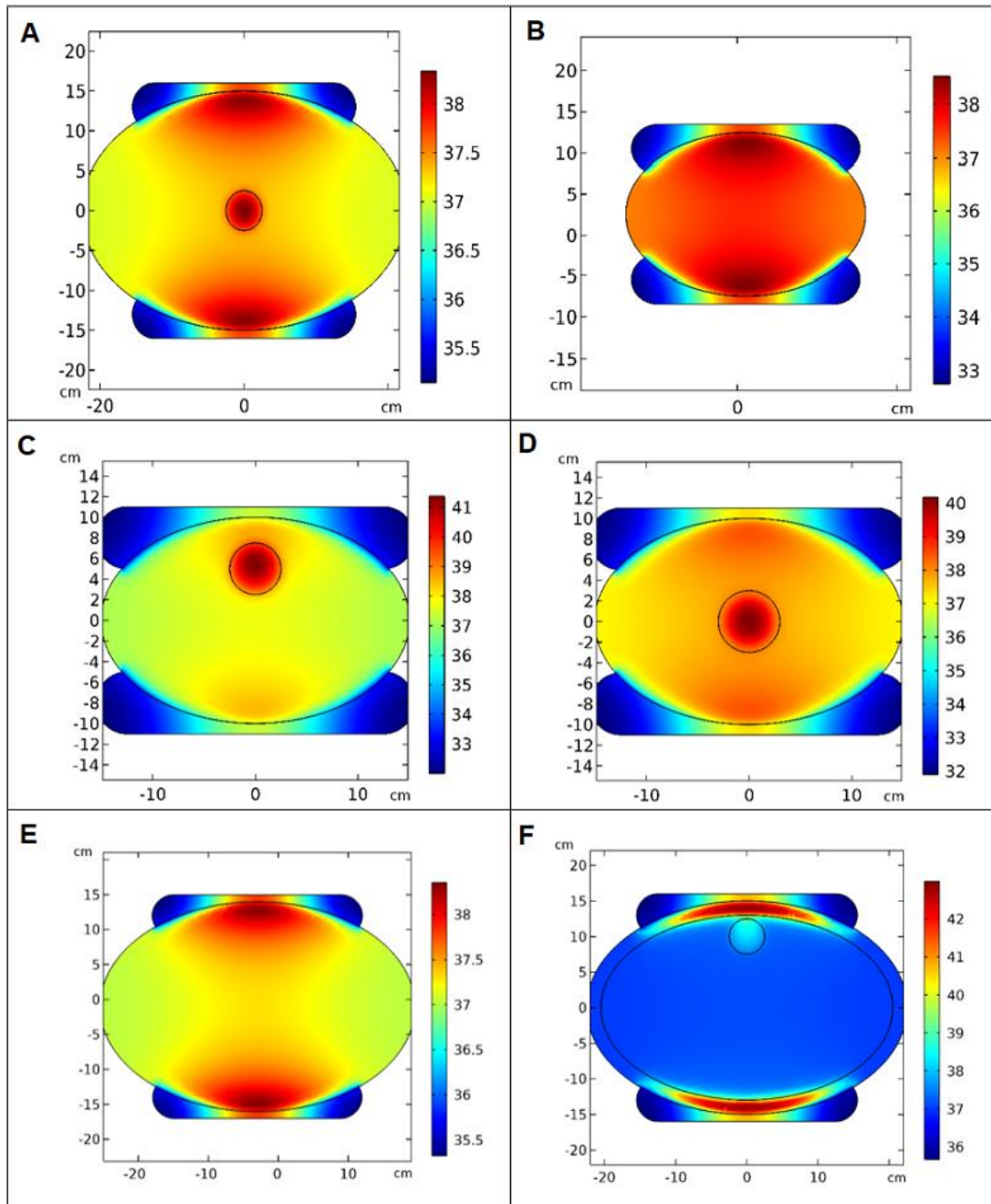


Figure 4. Heat map temperature distribution in various cases: A) Large size without tumor, B) Large size with superficial tumor, C) Large size with deep-seated tumor, D) Small size without tumor, E) Small size with superficial tumor, and F) Small size with deep seated tumor

model, simple geometric shapes were used to determine the patient's body and the area of the tumor, and this simplification increases the error in the simulation calculations. Therefore, using CT scan images can compensate for this error. In Figure 6, a scan is selected from a CT scan image and irradiated with 150 watts of capacitive hyperthermia for one hour. In Figure 6A, according to the application of electrical properties of the tissues, the rate of

temperature increase of those tissues is placed. As the Figure 6 shows, adipose tissue has the highest rate of temperature rise. Then the bone tumor tissue is in the next step and these is related to physical parameters such as the thermal conductivity of the mentioned tissues. In addition, according to Figure 6D, the

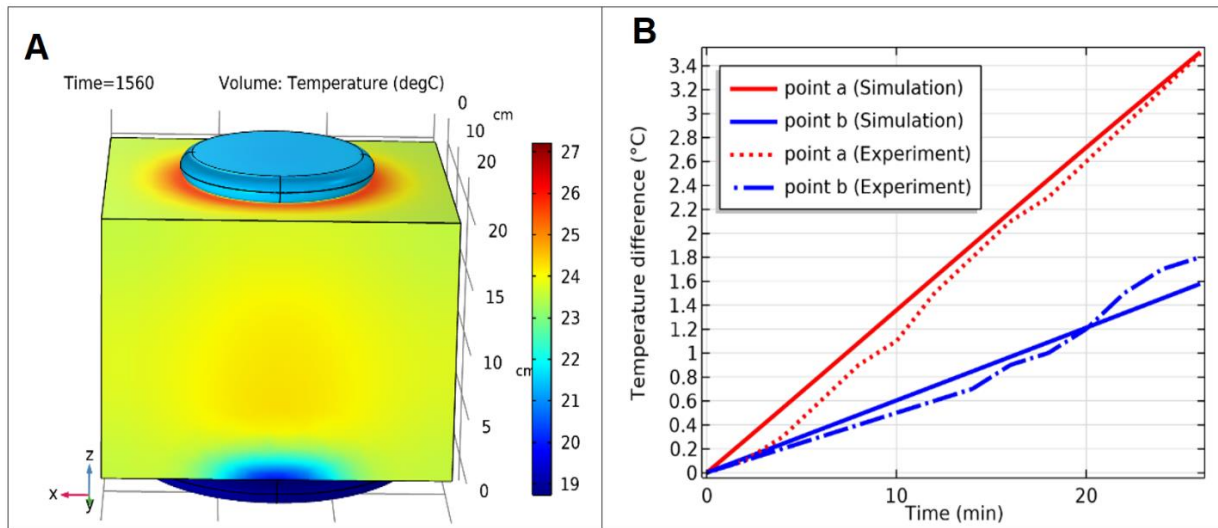


Figure 5. A) Simulation of temperature distribution in experimental phantom, B) Comparison of the results of simulation of temperature distribution in the specified points (work done in this study) with the data obtained from the thermometry of the study conducted by Sahinbas *et al.* [4]

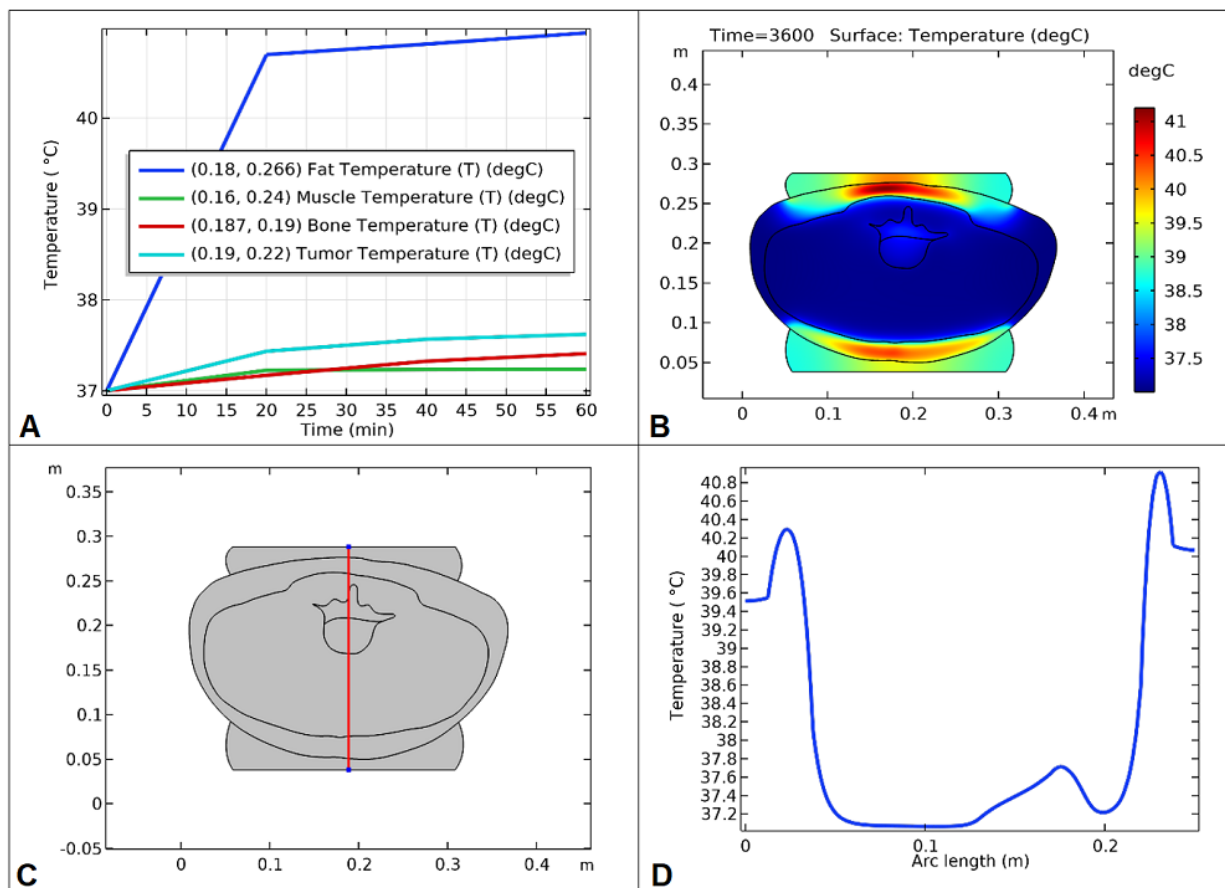


Figure 6. A) The rate of increase in temperature over time for different tissues, B) The temperature distribution map for the real model that has been exposed to capacitive heating for one hour, C) The red line indicates the temperature measurement path, and D) Temperature variation during irradiation for one hour from the patient's back to the patient's abdomen (red line in C panel)

clinical thermal map also showed that large patients are difficult to warm up and as for phantom

simulations, better target heating was simulated for smaller patients with capacitors hyperthermia.

4. Discussion

Today, the potent adjunctive treatment for cancer, along with radiotherapy and chemotherapy, is hyperthermia [7, 24]. Among the types of hyperthermia methods, as a non-invasive and deep method, we can mention radio frequency wave hyperthermia [17, 25]. Among the challenges in this method are the lack of uniform heat distribution as well as heat measurement and temperature control during treatment [5, 26]. One of the most important challenges of this method is the non-uniform distribution of heat as well as heat measurement and temperature control during treatment [19, 27]. For pelvic cancer, the efficacy of hyperthermia has been clinically demonstrated in a number of clinical trials. Unfortunately, the technology used in these studies only provides limited thermal dose control, and the devices used only help treat target areas close to the skin.

Our strategy involves providing a three-dimensional model for numerical modeling using the finite element method to estimate the temperature distribution in the patient's body and the tumor caused by electromagnetic waves generated by two capacitive applicators. This 3D model is based on CT images, which allows the patient's tumor shape to be accurately entered into simulation calculations so that we can achieve a suitable treatment model. In this study, a comparison of temperature distributions in small and large fat tissue phantoms as well as obese and lean patients showed that capacitive hyperthermia is generally more effective in heating deep-seated pelvic tumors for small samples than large samples, where simulation had similar results. Studies by Kok *et al.* on the treatment of patients with deep-seated tumors such as pelvic and prostate cancers by capacitive and radiative hyperthermia have shown similar results [7, 8]. However, their studies showed that the treatment of radiofrequency hyperthermia with antennae is more effective than capacitive hyperthermia and has a better effect on increasing the depth temperature of the tumor. In addition, their studies showed that placing electrodes at the top and bottom of the phantom was clearly more effective than heating with electrodes on either side, which could be similar to heating a smaller phantom due to the shorter distance to the target. This is confirmed by the results

of our experimental and simulation experiments (Figures 5 & 6D). Similar results have been reported by Kroeze *et al.* for a patient with prostate cancer in heat treatment [28]. Also, studies by Sahinbas *et al.* on phantom agar have also shown that for very thin and almost fat-free patients, capacitive hyperthermia can be an effective loco-regional therapy for deep tumors [6].

There are several challenges to verifying the temperature distribution in the phantom [29, 30]. For experimental instruments, the measurement error of the thermocouple or the uncertainty of the frequency of the radiant radio waves must be considered. On the other hand, simplifications in solving the equations of bio-thermal heat and electric current are among the factors that affect the simulation errors. Therefore, for the reasons mentioned, a simulation is not without free and many parameters are involved in the study. In Figure 5, the data related to the comparison of the two simulation and experimental studies are presented. The error rate of the above method causes a sudden increase in temperature. On the other hand, after the temperature equilibrates, this temperature slope decreases and at higher times, the accuracy of the models is very promising. This simulation method makes it possible to predict possible temperature changes of the tumor and the careful selection of heating equipment for patients.

5. Conclusion

The results obtained from the experimental measurement are in good agreement with the theoretical phantom simulation. The simulation results showed that therapeutic temperatures for capacitive hyperthermia are more predictable in lean patients than in obese patients. Therefore, developing the simulation methods can be used to predict temperature changes during the treatment of capacitive hyperthermia.

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