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Parametric sensitivity analysis of critical factors affecting the thermal damage during RFA of breast tumor

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ABSTRACT

A sensitivity analysis has been conducted to quantify the relative influence of several critical parameters on the size of ablation volume generated during temperature-controlled radiofrequency ablation (RFA) of breast tumor. In order to minimize the number of experiments, Taguchi's L16 orthogonal array has been utilized to determine the effect of four parameters with 4-levels each. The parameters considered are breast density composition, target tip temperature, tumor blood perfusion rate and location of tumor from body core. A three-dimensional heterogeneous numerical model of breast with a spherical tumor of 2.2 cm has been developed for this purpose. Temperature-controlled RFA has been performed by incorporating the closed-loop feedback proportional-integral-derivative (PID) controller in the numerical model using monopolar multi-tine electrode. The size of the tumor ablation volume has been taken as the response variable that has been obtained from finite element analysis by incorporating the coupled electric field distribution, the Pennes bioheat equation and the first-order Arrhenius rate equation. A non-linear piecewise model of blood perfusion has been considered to achieve better correlation with the clinical RFA. Also, the effects of temperature-dependent changes in electrical and thermal conductivity have been incorporated. Further, analysis of variance (ANOVA) has been performed to quantify the ranking and contribution of each parameter on the size of ablation volume produced during RFA. The results obtained from the numerical study revealed that the target tip temperature and tumor blood perfusion, followed by breast density composition, have a maximum influence on the ablation volume generated during temperature-controlled RFA.

1. Introduction

Breast cancer is a malignant tumor that occurs when cells in the breast grow out of control and form a lump. Breast cancer usually flourishes in the lobules that produce milk or the ducts which supply milk, and very rarely in the stromal tissues, which include fatty and fibrous connective tissues of the breast [1]. Globally, breast cancer is the second most common type of cancer after lung cancer and the fifth most common cause of cancer death [2]. In 2012, an estimated 1.67 million new cases were diagnosed with breast cancer, and close to 5.22 million deaths estimated to have occurred due to breast cancer worldwide [2]. Breast cancer is the most frequently diagnosed malignancy in the women worldwide with leading cause of mortality. Collectively, US, China and India account for almost one third of the global breast cancer burden [2]. In the year 2012, there were estimated 2,32,714, 1,87,213 and 1,44,937 new breast cancer cases diagnosed in the US, China and India, respectively, with India having the highest mortality rate (70,218 deaths) [2].

Several minimally invasive thermal ablative techniques are available in clinical practices that utilizes a fatal high or low temperatures to induce irreversible cellular injury and coagulative necrosis of tumor cells. Based on the energy sources and their delivery, the thermal ablative techniques can be classified into five major categories, viz., radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA), cryoablation and high-intensity focused ultrasound (HIFU) ablation [3]. Among these different thermal ablative modalities, RFA has already shown to be the most promising, extensively studied and widely applied technique in clinical practices for the treatment of primary hepatocellular carcinoma and colorectal metastasis of the liver. Also, RFA technique is gaining interest in the treatment of solid tumors in lung, brain, kidney, prostate and bone [4–7]. During RFA, high-frequency alternate current (450–550 kHz) is delivered into the tumorous tissue with the aid of electrode to induce frictional heating that irreversibly destroys the tumor cells by instantaneous induction of protein coagulation. With the developments in past several decades, RFA has become an alternative treatment modality to treat early and small tumors in those patients for whom surgery is not a viable option. Further, RFA is a cheap and faster technique that results in associated reduction

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Nomenclature

A	frequency factor (s^{-1})
c	specific heat capacity (J/kg K)
e	error
E_a	activation energy (J/mol)
k	thermal conductivity (W/m K)
K_d	derivative gain
K_i	integral gain
K_p	proportional gain
Q_m	metabolic heat generation (W/m^3)
Q_p	radiofrequency heat source (W/m^3)
R	universal gas constant
S/N	signal to noise ratio
t	time (s)
T	temperature (K)
V	electric potential (V)
V_i	ablation volume for experiment i (mm^3)

Greek symbols

ρ	density (kg/m^3)
σ	electrical conductivity (S/m)
ω	blood perfusion (s^{-1})
Ω	induced thermal damage

Subscripts

b	blood
0	initial value

Abbreviations

ANOVA	analysis of variance
ED	extremely dense
HD	heterogeneously dense
PID	proportional-integral-derivative
PF	predominantly fatty
RFA	radiofrequency ablation
SF	scattered fibroglandular

in mortality, morbidity and recovery time with improved cosmesis as compared to other treatment modalities [5,7].

The application of RFA in treatment of breast cancer is still a developing area of research with most of the studies reported in the past decade limited only to assess its safety and feasibility [8]. Moreover, breast as an organ has been considered as an ideal model for RFA application because of its superficial location in the thorax and due to the absence of intervening organs. The first study on application of RFA in the treatment of human breast cancer was performed way back in year 1999 by Jeffrey et al. [9], on 5 women (aged 38–66 years) having locally advanced (stage III) invasive breast cancer with a success rate of 80%. It was concluded from the study that RFA can be effectively used for treatment of primary breast tumors having diameter less than 3 cm. Further, an extensive literature survey conducted by Zhao and Wu [10] on minimal invasive thermal damage of early-stage breast cancer highlights that the clinical success rates of complete tumor ablation using RFA is 76–100% as compared to microwave ablation (0–8%), laser ablation (13–76%), cryoablation (36–83%) and high-intensity focused ultrasound (20–100%).

Numerous computational studies are available in the literature on mathematical modeling of RFA that play a vital role in providing *a priori* information about the possible outcomes and risks involved to clinical practitioners before the onset of RFA. However, majority of these studies are mainly focused on the liver investigating either a one- or two-compartment models. Only a handful of studies are available on application of RFA in breast cancer [11–15] due to the complexity associated in modeling heterogeneous breast model that comprises of varying concentrations of fat, glandular and connective tissues. According to BI-RADS (Breast Imaging Reporting and Data System), different breast density levels for women can be classified into four main categories, in order of increasing percentage of fatty tissue, viz., extremely dense (ED), heterogeneously dense (HD), scattered fibroglandular (SF) and predominantly fatty (PF) [16]. The individual percentage variations of glandular and fatty tissues may lead to significant variations in the ablation volume during RFA, since each tissue has different thermo-electric properties. Further, there is a wide range of variability in the blood perfusion rate of breast tumor from 5.3×10^{-3} to 5.3×10^{-2} s^{-1} [17] that may significantly affect the ablation volume produced during RFA.

Since the efficacy of RFA is mainly judged by the size of ablation volume produced, so it becomes very important to identify the critical factors that influence the size of ablation volume produced during RFA. Thus, the aim of the present work is to investigate the effects of four critical parameters, viz., breast density composition, target tip temperature, tumor blood perfusion rate and location of tumor from body core, on the size of ablation volume utilizing Taguchi's design of experimental methodology. Further, analysis of variance (ANOVA) has been performed to quantify the ranking and contribution of above mentioned critical parameters on the size of ablation volume produced during RFA. The responses of each experiment have been obtained from finite element based thermo-electric analysis of temperature-controlled RFA on the improved heterogeneous mathematical model of realistic human breast.

2. Materials and methods

2.1. Description of the model

In the present study, a heterogeneous three-dimensional model of breast (*refer* Fig. 1) has been considered [18] in which a spherical tumor of 2.2 cm diameter has been embedded to mimic breast tumor in early stages. The nine-tine RITA Starburst XL electrode (AngioDynamics Inc., Latham, NY) deployed to 2 cm manufacturer's setting has been inserted in the numerical model of breast such that the tip of electrode is 1 cm

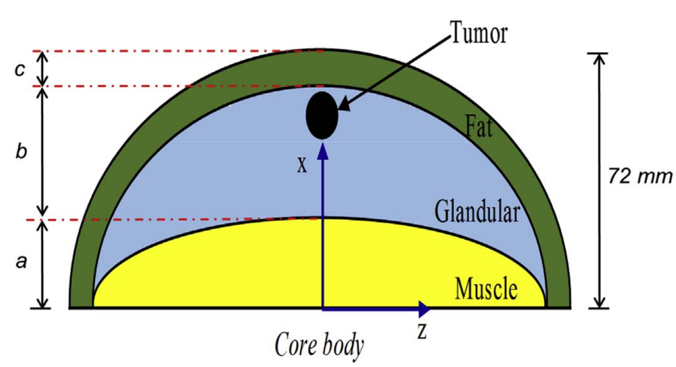

Fig. 1. Cross-sectional view of heterogeneous breast model. The values of a, b and c (in mm) for different breast density compositions have been considered to be 15.5, 54 and 2.5 for ED; 16.9, 49.6 and 5.5 for HD; 20.5, 40.4 and 11.1 for SF; 16.1, 32 and 23.9 for PF breast models, respectively.