Pre-clinical Modelling and Simulation of Hepatic Radiofrequency Ablation

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Abstract: Radio-Frequency ablation (RFA) has received a considerable interest as a minimally invasive treatment technique used for destruction of a variety of primary and metastatic hepatic tumors. A parametric study of hepatic radio-frequency ablation using three-dimensional numerical models has been done in order to determine the optimal value of applied energy (in terms of power and treatment time) adequate to ablate the target tumor for different stages of liver cancer. The induced thermal damage has been quantified by employing the first-order Arrhenius rate equation. Effects of variable conductivity and blood perfusion have also been addressed in this study. The finite element analysis revealed that, the effective damage of tumor volume depends on input power, treatment time and tumor size. It has been confirmed that temperature isotherms and tissue damage patterns are not synonymous. These results may be useful to provide a practical and fast guidelines to clinical practitioners.

Keywords: Radiofrequency ablation, Hepatic tumor, Bioheat equation, Finite element analysis

1. Introduction

Cancer is a leading cause of mortality worldwide, with 8.2 million deaths in 2012 [1]. Primary liver cancer is the sixth most frequent cancer globally and the second leading cause of cancer mortality after lung cancer [1]. Minimally invasive thermal ablation techniques have become common with the advancement in modern imaging [2]. Out of all the thermal ablative techniques, radio-frequency ablation (RFA) is the widely studied minimal invasive treatment method for inoperable cancer of liver. The current method possesses number of benefits, viz., decreased risk of complications from anesthesia, improved cosmesis and shortened recovery time, which may lead to decrease in morbidity and mortality of patients. During RFA, one or more electrodes are inserted percutaneously into the tumorous tissue with the help of image guidance techniques like ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). Once positioned, high-frequency alternating current (450–550 kHz) is delivered through these electrodes into the tissue that induces frictional (resistive) heating generated by intracellular ions moving in response to change in direction of an alternating current [2]. This frictional heating causes destruction of tumor cell by instantaneous induction of protein coagulation that irreversibly damages key cytosolic and mitochondrial enzymes and nucleic acid histone complexes at a higher temperature above 50 ^{0}C [3]. Interestingly, the higher temperatures should be strictly below 100 ^{0}C to avoid tissue carbonization and water vaporization that increases the tissue impedance thereby limiting further electrical conduction through the remaining tissue. Additionally, RFA planning is hampered if the ablated tumor is near the large blood vessels that causes a heat sink effect, and thus decreases the ablation volume [4].

The continuous improvement of numerical models of heat transfer in living tissues has been a topic of vital interest for various biologists, physicians, mathematicians and engineers. Theoretical models and computer simulations could be powerful tools in order to investigate and develop new techniques, and also to improve the existing techniques currently employed, as these would provide vital information on the electrical and thermal behaviour of ablation rapidly and at a low cost. Therefore, there is a great demand for the simulation tools that provide a good source of pre-clinical information. In the present work, three dimensional pre-clinical modelling and simulation has been done to determine the optimal power and treatment time for different stages of liver cancer. The heat transfer

phenomenon within the liver tumor due to the coupled effect of blood perfusion and variable conductivity during RFA has been investigated. The induced thermal damage and the treatment time required to achieve complete necrosis have been determined by employing first-order Arrhenius rate equation, addressing various issues like local heating and ablating tumor sparing healthy tissue.

2. Governing Equations and Boundary Conditions

A quasi-static approximation has been assumed to solve the electro-magnetic problem, since, in the frequency range of 450–550 kHz the wavelength of the electromagnetic field is several orders of magnitude larger than the size of the active electrode. The electric field distribution within the tissue due to applied voltage on RF electrode can be computed by using the generalized Laplace equation that can be written as

$$\nabla \cdot \left(\sigma \nabla V \right) = 0 \tag{1}$$

where σ is the electrical conductivity and V is the electric potential.

The electric field intensity (E) and the current density (J) generated within the tissue can be computed from

$$\begin{aligned} \mathrm{E} &= -\nabla V \\ \mathrm{J} &= \sigma \mathrm{E} \end{aligned} \tag{2}$$

The local power density that results in tissue heating is the product of current density (J) and electric field intensity (E) and can be written as

$$\mathrm{J.E} = \sigma . \mathrm{E}^2 \tag{3}$$

The temperature within the liver tissue subjected to electric heating during RFA has been evaluated by using well known Pennes bioheat equation [5]

$$\rho c \frac{\partial T}{\partial t} = \nabla \left(k \nabla T \right) - \rho_b c_b \omega_b \left(T - T_b \right) + Q_m + J.E \tag{4}$$

where ρ, c and k are the density, the specific heat and the thermal conductivity of the tissue, respectively, ω_b, ρ_b and c_b are the perfusion rate, the density and the specific heat of blood, respectively, Q_m is the heat generated due to metabolic activity, which has been assumed to be negligible and, J is the current density and E is the electric field intensity, T_b is the core blood temperature (assumed to be 37 ^{0}C) and T is the unknown tissue temperature.

The electrical conductivity dependence on temperature has been calculated from

$$\sigma \left(T \right) = \sigma_0 \left[1 + \alpha_\sigma \left(T - T_c \right) \right] \tag{5}$$

where σ_0 is the constant electrical conductivity at core body temperature, T_c = 37 ^{0}C. The temperature coefficient (α_σ) in the present study has been assumed to be 1.5% per ^{0}C for both liver and tumor tissues [6].

Earlier studies using RFA [7] suggested that, blood perfusion (ω_b) within the tumor is more than the surrounding healthy tissue and is assumed to be increasing initially due to vasodilation of capillaries caused by heating of perfused tissue [8], and later decreases with time/induced damage.

$$\omega_b \left(t \right) = \begin{cases} \omega_{b,0} & \text{for } \Omega \left(t \right) \le 0 \\ \omega_{b,0} \left[1 + 25\Omega \left(t \right) - 260\Omega \left(t \right)^2 \right] & \text{for } 0 < \Omega \left(t \right) \le 0.1 \\ \omega_{b,0} \exp \left[-\Omega \left(t \right) \right] & \text{for } \Omega \left(t \right) > 0.1 \end{cases} \tag{6}$$

where $\omega_{b,0}$ is the constant blood perfusion of tissue given in Table 1 and $\Omega(t)$ is the induced thermal damage.

The induced damage (or damage integral) has been computed using the well-established first order Arrhenius equation [9].

$$\Omega \left(t \right) = ln \frac{C_0}{C_{UD} \left(t \right)} = \int A exp \left[- \frac{E_a}{RT \left(t \right)} \right] dt \tag{7}$$

where C_0 is the original concentration of undamaged cells, C_{UD} is the concentration of remaining living cells after time t, the treatment time, A is the frequency factor, E_a is the activation energy and R is the universal gas constant (= 8.314 J mol^{-1} K^{-1}). In the present study, A and E_a for the bulk tissue domain have been considered as 2.984×10^{80} s^{-1} and 506400 J mol^{-1}, respectively [6]. In the context of tissue

damage, a damage integral of $\Omega = 1$, corresponds to 63% percent probability of cell death and damage integral of $\Omega = 4.6$, corresponds to 99% percent probability of cell death at a specific point. A damage integral of $\Omega = 1.0$ (corresponds to 63 % probability of cell death) has been assumed to be the point at which tissue undergoes irreversible damage of constituting proteins and cell organelles [9].

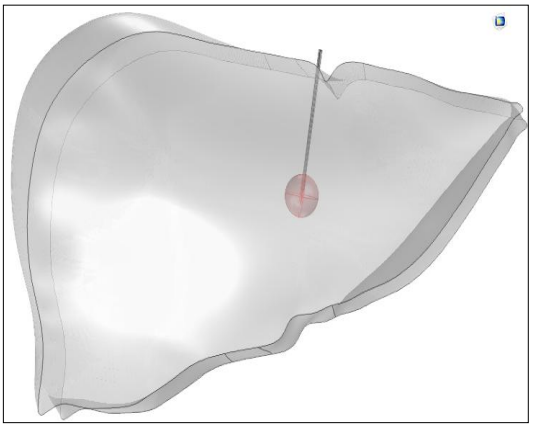

Figure 1. Schematic of simulating hepatic radiofrequency ablation in 3-D model using COMSOL®

Figure 1 shows the schematic of three dimensional two-compartment model comprising of liver, tumor and electrode. The model of real human liver has been constructed based on the anatomical details available in the literature [10]. A spherical tumor of varying diameter (D< 5 cm) of stage T1 of TNM (Tumor, Node, Metastasis) based on staging guidelines given by American Joint Committee for Cancer Staging (AJCCS) [10] has been embedded into the liver. Furthermore, the tumor diameter (D) has been varied to consider two stages, viz., stage 0 ($D < 2$ cm) and stage A ($2 \text{ cm} \leq D < 3$ cm) based on the staging guidelines given by Barcelona Clinic Liver Cancer (BCLC) staging system [11]. Table 1 depicts the electrical as well as thermal properties of liver, tumor, electrode and trocar insulator at 500 kHz [12, 13]. The mono-polar electrode [14] is 77 mm long with a diameter of 1 mm. The distal part (i.e., 7 mm) of the probe was an electrically conductive metal (stainless steel), and the proximal part (70 mm) of the probe was covered with an electrically insulating material (teflon).

Table 1: Thermal and electrical Properties (500 kHz) [12, 13].

Tissue	σ, *S/m*	c, *J/kg.K*	k, *W/m.K*	ρ, kg/m^3	ω_b, s^{-1}
Liver	0.333	3600	0.512	1060	0.0017
Tumor	0.1168	4200	0.552	999	0.0156
Electrode	9.8×10^5	500	36.7	8100	–
Trocar	10^{-16}	1010	0.23	2190	–

3. Simulation Methodology

The three dimensional CAD model of liver has been imported to COMSOL Multiphysics 5.1. The tumor and the mono-polar electrode have been constructed using geometry interface of COMSOL and has been embedded inside the CAD model of liver. The initial voltage of the entire tissue domain before the onset of RF energy has been considered to be zero. The electrical voltage boundary condition for the grounded outer periphery of liver tissue has been set to be zero. Electrical insulation condition has been set for the portion of insulated trocar inside and outside the tissue domain. The electrode potential has been set to a constant source potential (V) ranging between 10-30 V. The initial temperature of liver tissue has been considered to be same as that of the core body temperature (= 37 ^{0}C). For numerical simulations, the specific heat and density of blood have been considered to be 4180 $Jkg^{-1}K^{-1}$ and 1050 kgm^{-3}, respectively. In the present study, electric currents (ec) physics of AC/DC module, bioheat transfer (ht) physics of Heat Transfer module and domain ODEs and DAEs (dode) of mathematics module of COMSOL Multiphysics have been used to solve the FEM problem.

The meshing of physical domain has been done using fine tetrahedral mesh elements, i.e., 1,87,679 tetrahedral elements. The maximum element sizes of liver, tumor, electrode and trocar have been considered to be 0.3 cm, 0.05 cm, 0.05 cm, 0.05 cm, respectively. The above mesh element sizes have been determined after several runs with varying number of mesh elements and identical properties to attain a grid

independent solution, i.e., the absolute error in tumor temperature nearby the tip of the electrode is negligibly small between the two consecutive sizes of mesh elements. The relative tolerance for the electric field interface and heat transfer interface has been set to 0.0001. A coupled thermo-electrical analysis during RFA of cancerous liver tumor has been performed using COMSOL Multiphysics® 5.1. Computations have been performed on an Intel® Xeon® processor (10 core) having 3.1 GHz clock speed and 64.0 GB RAM.

4. Results and Discussion

The heating of tumor volume during RFA depends on tissue properties, tumor shape, applied voltage, heating time, probe location within the tumor, etc. Out of all these factors, the treatment time and applied voltage play a vital role [15] which need to be optimized for different stages of hepatic cancers during RFA. In order to determine the role of source voltage and tumor size in treatment efficacy, three different tumor diameters 1, 1.5 and 2 cm based on T1 stage of hepatic cancer have been considered in accordance to the staging guidelines given by AJCCS [10] and the applied voltage values have been varied between 10-30 V in the present study. In addition to keeping maximal ablation temperature below 100 ^{0}C to avoid tissue charring and carbonization, optimization of the applied energy (in terms of power and treatment time) was dictated by the following criteria: (i) complete ablation of tumor and (ii) minimal collateral damage to the surrounding healthy tissue [15].

To evaluate the optimal voltage and desired treatment time for complete tumor necrosis, a detailed sensitivity study has been performed by varying the applied voltages (10-30 V) for different tumor diameters. The optimal values of applied voltages along with the time taken to reach damage integral of entire tumor to Ω = 1 and Ω = 4.6, corresponding to 63% and 99% probability of cell death, respectively, for different tumor diameters have been presented in Table 2. The optimal values have been judiciously selected based on the simulation results, so that minimum ablation time is 3 min and maximum ablation time is 20 minutes, with an additional constraint of keeping the maximum temperature below 100 ^{0}C. The applied voltage between 10-15 V have been found to be insufficient for complete necrosis of tumor of all diameters even after hours of treatment time. On the other hand voltages in the range of 25-30 V have been found to be producing complete tumor necrosis within few seconds for tumor diameter of 1 cm which can be quite risky. Since, the response time is too short and excessive unwanted damage could be evident in clinical practices. It can be seen from Table 2 that the increase in tumor diameter leads to an increase in the required treatment time and applied voltage, since the thermogenic capacity of tumor increases with increase in tumor diameter.

Table 2: Optimal voltage and treatment time for different tumor diameters during RFA.

Tumor Diameter	Optimal Voltage	Time to reach Ω =1	Time to reach Ω =4.6
D = 1 cm	20 V	4.7 min	7.2 min
D = 1.5 cm	25 V	8.4 min	12.9 min
D = 2 cm	30 V	12.7 min	18.7 min

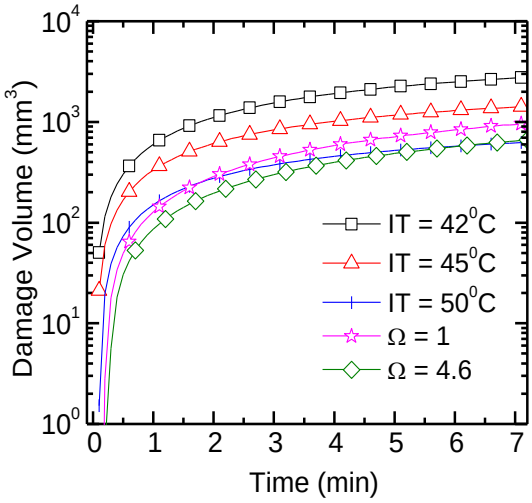

Figure 2. Total volume of tissue necrosis using thermal damage integral (Ω) and isothermal temperatures (IT).

The produced necrosis volume has been shown in Fig. 2 for 1 cm diameter tumor with applied voltage of 20 V up to treatment time of 7.2 minutes until Ω = 4.6 (i.e. 99% cell damage) is

achieved. It can be clearly seen from Fig. 2 that, isothermal fronts, viz., IT 42 and IT 45 overestimate the amount of tissue injury during RFA which should not be the case otherwise as was mentioned in [12]. It has been further verified that temperature isotherms and tissue damage patterns are not synonymous in RFA application similar to the results presented in [6].

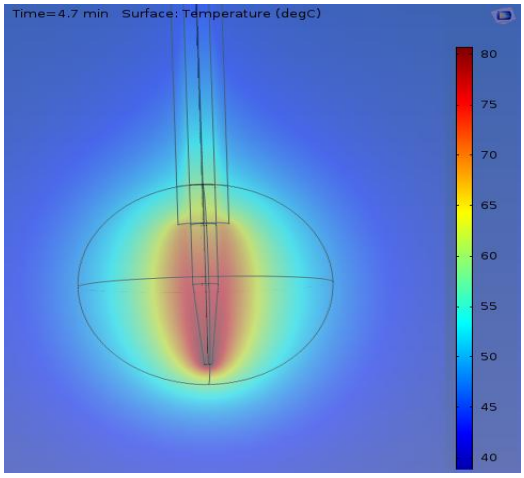

Figure 3. Temperature distribution for 1 cm diameter tumor with 20 V after 4.7 minutes.

Figure 3 shows the temperature distribution for 1cm diameter case with applied voltage of 20 V till the time required (i.e., 4.7 minutes) for the entire tumor to reach the thermal damage integral of $\Omega \geq 1$.

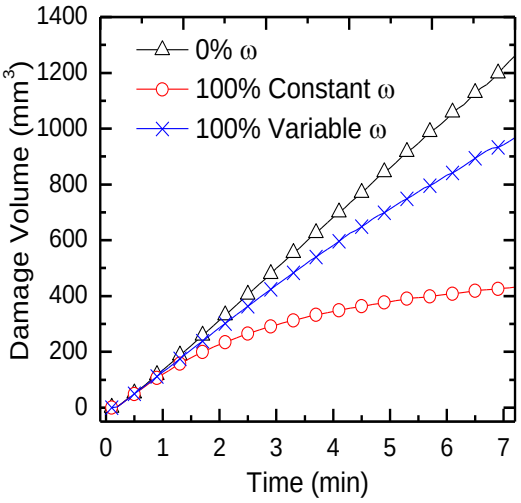

Figure 4. Effect of perfusion on lesion volume corresponding to thermal damage integral $\Omega \geq 1$ with time.

The effect of blood perfusion on lesion volume produced for 1 cm diameter case with applied voltage of 20 V during RFA has been shown in Fig. 4. It can be seen from Fig. 4 that, ablation volume is overestimated with zero perfusion of tumor and healthy tissue when compared to 100% constant perfusion case. Furthermore, during RFA blood perfusion changes due to gradual necrosis of cells with time and is mainly due to leftover undamaged cells. The perfusion is assumed to be increasing initially due to vasodilation of capillaries caused by heating of perfused tissue and later decreases with time/induced damage as given by Eq. (6). The comparison of this varying perfusion with the constant perfusion in terms of necrosis volume has also been shown in Fig. 4. It can be clearly interpreted form Fig. 4 that, the constant blood perfusion value within the tissue underestimates the lesion volume produced as compared to the varying blood perfusion case.

It can be seen from Fig. 5 that, the increase in blood perfusion within the tumor causes a greater cooling effect due to which the ablation temperature and time required for ablating tumor are considerably more compared to the healthy tissues. Hence, blood perfusion within the tumor and the tissue has a great influence on both lesion volume and achievement of maximum temperature during RFA.

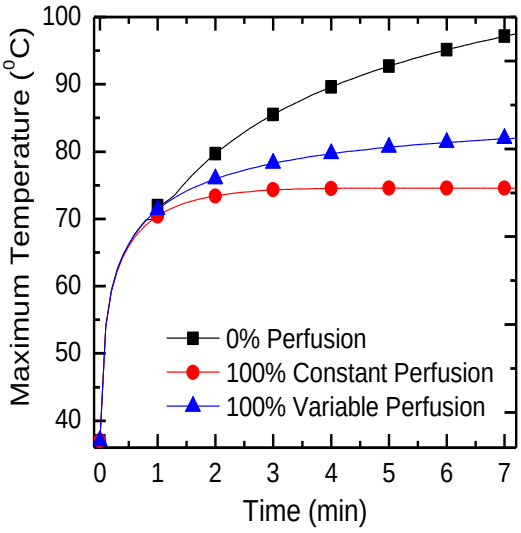

Figure 5. Effect of perfusion on maximum temperature achieved during RFA with time.

Figure 6 depicts the effect of variable electrical conductivity on maximum temperature produced with 20 V power and 1 cm tumor diameter. It can be seen from Fig. 6 that, the maximum temperature is slightly higher in the case of varying electrical conductivity when compared with constant electrical conductivity case. This effect is more pronounced at a higher temperature above 100 ^{0}C. The maximum error associated with the assumption of constant electrical conductivity has been found to be ≤ 0.02 %.

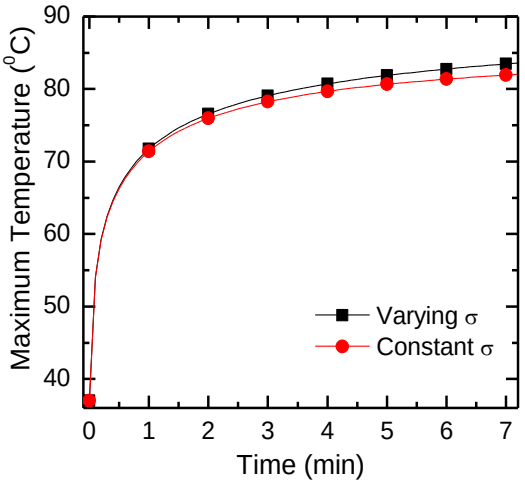

Figure 6. Effect of variable electrical conductivity on maximum temperature achieved with time.

5. Conclusions

A parametric study has been performed on three-dimensional FEM models of liver having different stages of liver cancer by including the effects of blood perfusion (both in tissue and tumor) and variable conductivity during RFA. The voltage and treatment time have been optimised for different stages of tumor on the basis of thermal damage front to achieve a good control during clinical RFA. It has been found that, the increase in thermogenic capacity due to increase in tumor volume causes a significant increase in the treatment time for a particular applied voltage. The study further revealed that, blood perfusion has an immense effect on lesion volume produced and should not be neglected while modeling RFA. Moreover, it is warrant to mention that, the tumor perfusion is more significant than the surrounding tissue perfusion during RFA. Further, it has been verified that the lesion volume produced by damage front and conventional isotherms are not synonymous and the size of thermal lesions is grossly overestimated when calculated using isotherms. The simulation results revealed that the effect of constant electrical conductivity compared to varying electrical conductivity on maximum temperature is negligible small during RFA. The present results of pre-clinical modelling and simulation of hepatic cancer, along with patient-specific models can be used to provide a practical and fast guideline to clinical practitioners during RFA.

6. References

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