Applied Thermal Engineering 90 (2015) 296–304

Contents lists available at ScienceDirect

Applied Thermal Engineering

journal homepage: www.elsevier.com/locate/apthermeng

Research paper

Three-dimensional numerical simulation of the effects of fractal vascular trees on tissue temperature and intracelluar ice formation during combined cancer therapy of cryosurgery and hyperthermia

Zhen Wang [a], Gang Zhao [a, b, *], Tao Wang [a], Qianfeng Yu [a], Minying Su [c], Xiaoming He [d, **]

[a] Centre for Biomedical Engineering, Department of Electronic Science and Technology, University of Science and Technology of China, Hefei 230027, China
[b] Anhui Provincial Engineering Technology Research Center for Biopreservation and Artificial Organs, Hefei 230027, China
[c] Departments of Radiological Sciences and Physics, University of California, Irvine 92697, USA
[d] Department of Biomedical Engineering, The Ohio State University, Columbus, OH 43210, USA

HIGHLIGHTS

- A three-dimensional cell-to-tissue multiscale model was successfully developed.
- The fractal vascular tree was constructed based on MRI images.
- The numerical method is verified by previously works that have been published.
- The model assess the impact of the vascular network on the treatment outcome.
- The damage functions and intracellular ice formation evaluate cancer destruction.

ARTICLE INFO

Article history:
Received 7 April 2015
Accepted 28 June 2015
Available online 11 July 2015

Keywords:
Bioheat transfer
Cryosurgery
Hyperthermia
Vascular network

ABSTRACT

A three-dimensional cell-to-tissue multiscale model for quantitative evaluation of the influences of vascular network on the treatment outcome of combined cancer therapy of cryosurgery and hyperthermia was developed, where the bioheat transfer equation was used to predict the thermal history in both the tumor and normal tissues, the Navier–Stokes equations were used to calculate the temperature and flow fields in the vascular network generated using fractal theory based on MRI images, and the thermal and cryo damage functions together with the injury caused by intracellular ice formation were used for evaluating the killing effect. The effects of the vascular tree on both the thermal history and intracellular ice formation in the tissues were investigated. For a tumor located at the first level of vascular network, the vascular network is significant only when the distance between the tumor and blood vessel is less than three times of the radius (R) of the tumor and this critical distance decreases to 2R for the second level of the vascular tree. For a fixed distance between tumor and blood vessel, the first level of vascular network was found to be thermally significant while the third or lower levels of vascular tree are not.

1. Introduction

Developing effective strategies to treat cancer has been an important task in the field of medical research globally [1]. With the advancement of cryoprobe and *in vivo* imaging technologies in the past two decades, both extreme low (for cryosurgery, cryoablation, or cryotherapy) and high (for hyperthermia or thermal therapy) temperatures have been utilized to minimally invasively and selectively destroy tumor in the clinic [2–7]. Furthermore, the combined therapy of cryosurgery and hyperthermia (i.e., freezing followed by heating) has attracted much attention for treating cancer with many advantages including low cost, reduced pain, minimally invasiveness, and likelihood of activating immune reaction that helps to kill tumor compared to radical surgical intervention [8–10].

* Corresponding author. Centre for Biomedical Engineering, Department of Electronic Science and Technology, University of Science and Technology of China, Hefei 230027, China. Tel.: +86 18256929838.
** Corresponding author. Department of Biomedical Engineering, The Ohio State University, Columbus, OH 43210, USA. Tel.: +1 614 247 8759.
E-mail addresses: ZhaoG@ustc.edu.cn (G. Zhao), he.429@osu.edu (X. He).

http://dx.doi.org/10.1016/j.applthermaleng.2015.06.103
1359-4311/

In cryosurgery, the freezing process could result in vascular injury, possible immunologic responses, and direct cellular injury that was a result of intracellular ice formation (IIF), recrystallization of intracellular ice, and thermal stresses [2,4,5,9,11–15]. Hyperthermia or thermal therapy has been shown to destroy cancer by damaging the cell membrane structure, activating the lysosomal enzymes activity, and inhibiting of DNA, RNA, and protein synthesis, and denaturizing proteins [5,9,16,17]. Due to the aforementioned multifaceted mechanisms of cancer destruction by cryosurgery and hyperthermia, a mechanistic model is still missing for predicting cancer destruction by either extreme low or high temperatures. As a result, a critical low or high temperature was conventionally used to judge tumor destruction for cryosurgery and hyperthermia, respectively. However, it is difficult to determine the critical temperature of hyperthermia therapy accurately, and studies reported in the literature suggest that damage at the cellular level could be used to predict the destruction of tumor during hyperthermia [18–20]. Accordingly, the cell survival rate was used to evaluate the efficacy of hyperthermia in this study.

Regardless of cryosurgery or hyperthermia, the network of blood vessels in tumor plays a significant role in determining the outcome of cancer treatment. It has been shown that vascular injury mainly occurs in blood vessels with a diameter less than 3 mm [21]. It has also been shown that the blood vessels of tumor are more sensitive to heat than normal vasculature [22–25]. Previous studies show that blood vessels had an effect on the thermal history in both normal tissue and tumor during cryosurgery and hyperthermia. For example, Zhao et al. [12] demonstrated the heating effect of thermal significant blood vessels in cryosurgery. Deng et al. [10] studied the effects of large blood vessels on the transient temperature field during combined therapy of cryosurgery and hyperthermia for four different arrangements between the blood vessels and the tumors. Shi et al. [26] constructed a simple two-dimensional vascular network model to study the bioheat transfer of biological tissue during cryosurgery. Zhang et al. [27] developed a two-dimensional microscale model for prediction of breast cancer cell damage during cryosurgery in the absence of blood vessels. While none of the previous studies have investigated the effect of the three-dimensional vascular network constructed from the clinical medical images on the combined hyperthermia/cryosurgery procedure. Moreover, few studies have used the probability of intracellular ice formation (PIF) as an indicator for killing of tumor cells. Furthermore, the thermally significant blood vessels have not been rigorously defined.

In this study, the fractal theory that has been widely used for solid modeling of human organs [28] was employed together with MRI images from a breast cancer patient to construct the 3D vascular network. A coupled heat transfer and fluid flow model was then established in the three-dimensional space consisting of tumor, normal tissue, and the constructed vascular network. This model was then used to predict the effect of vascular network on thermal history, intracellular ice formation, and tumor destruction during the combined treatment of cryosurgery and hyperthermia. Moreover, the thermally significant blood vessel was defined based on both the level of the vascular tree and the relative position between the tumor and the vascular network. The model established and the results obtained in this should be of significance for the treatment planning and probe design of both low and high temperature cancer therapies.

2. Solid model including the fractal structure of vascular networks

Vascular network exists in the three-dimensional space of different organs in human body. A typical magnetic resonance imaging (MRI) scan of a patient with breast cancer is shown in Fig. 1(a) and (b). It is evident that breast tumor is surrounded by a vascular network, including both symmetrical and asymmetrical vessels. Due to the complexity and diversity, realistic numerical representation of the vascular network is challenging [29,30]. The fractal structure is a simplified blood vessel network which has been shown to be sufficient for hemodynamic study [29]. In the fractal structure, the vascular network begins with a single vessel that divides into two segments and each of these parent segments in turn divides into two child segments till the end of the vascular network [26]. In this study, a simple symmetrical vascular network model was constructed according to the Murray's law [26], which is shown in Fig. 1(c). The parameters of diameter and length of each branching level of the vascular tree are given in Table 1.

For the vascular network, the change in diameter of parent and child vessels at branching nodes satisfies the Murray's law as follows [26,29,31]:

$$\lambda_0^x = \lambda_1^x + \lambda_2^x \tag{1}$$

where λ is diameter of the vascular network. The subscript 0 refers to the parent segment and 1 and 2 refer to the two child segment at the same bifurcation. The superscript x is used to describe the bifurcation exponent, and the value of x ranges from 2 to 3 for vascular network in the human body. However, for large arteries of systemic circulation, the bifurcation exponent is approximately 2.33 [29].

In the circulatory system, the length of the vascular branches is proportional to vessel diameter as follows [26]:

$$\ell = K \times \lambda \tag{2}$$

where K is a constant (20) for given vessels.

The angle of the two junction branches is an important feature of the geometric characteristics of vascular network. According to Murray's formula, it can be described as the following [26,29,31]:

$$\cos\phi_1 = \frac{\lambda_0^4 + \lambda_1^4 - \lambda_2^4}{(2\lambda_0\lambda_1)^2} \cdot \cos\phi_2 = \frac{\lambda_0^4 - \lambda_1^4 + \lambda_2^4}{(2\lambda_0\lambda_1)^2} \tag{3}$$

where $\lambda_0 = 3$ mm [29,32], $\lambda_1 = \lambda_2$, ϕ_1 is angle between child 1 and parent vessels, ϕ_2 is angle between child 2 and parent vessels, and the total branch angle $(\phi_1 + \phi_2)$ is known as bifurcation angle and its value should be between 75° and 90°. When two child vessels are symmetric, the total branch angle is 75° [29].

3. Physical model: heat-transfer and fluid flow analysis in biological tissue

3.1. Bioheat transfer

Heat transfer in the interstitial space of biological tissue can be predicted by the Pennes bioheat equation [31]:

$$\frac{\partial(\rho c T)}{\partial t} = \nabla\cdot(k\nabla T) + \rho_b c_b \omega_b (T_b - T) + Q_{met} \tag{4}$$

where c_b and c is effective thermal capacity of blood vessels and tissue, respectively, k is thermal conductivity, ρ and ρ_b are density of tissue and blood vessels, respectively, T_b is arterial temperature, ω_b is blood perfusion, and Q_{met} is metabolic heat generation (w/m^3).

The heat transfer and fluid flow in the vascular network is governed by the following energy, continuity, and momentum (i.e., Navier–Stokes) equations [31]:

The energy equation: