Laser Interstitial Thermo Therapy (LITT) for Prostate Cancer Animal Model: Numerical Simulation of Temperature and Damage Distribution

M. F. Marqa*[1,2], P. Colin[1,2,3], P. Nevoux[1,3], S. Mordon[1] and N. Betrouni[1,2]
[1]Inserm, U703, CHRU of Lille, Lille, 59037, France,
[2]University of Lille 2, Lille, 59037, France
[3]Department of Urology, CHRU Lille, Lille, 59037, France
*Corresponding author: Inserm, U703, 152, avenue of Dr. Yersin, 59120, Loos, France; email address: feras.marqa@chru-lille.fr

Abstract: Laser interstitial thermotherapy (LITT) is a cancer treatment technique in which laser fibers are introduced inside the tumor. While it destroys deep tumors, the LITT procedure allows minimizing the impact on adjacent healthy structures. Image guided focal photothermal ablation of low risk and low volume prostate cancer is feasible. However, dosimetry planning and conformation of the treated area within the tumor remain major issues, especially when, for large-sized targets, it is necessary to use several fibers. One of the effective methods to perform treatment planning for LITT is the simulation. We used COMSOL Multiphysics to simulate the heat distribution and thermal damage resulting from laser interstitial of a cylindrical diffusing fiber (CDF) in a biological medium. Simulation provided good estimation of the results of the *in-vivo* experiments.

Keywords: Laser interstitial thermotherapy, thermal damage, prostate cancer, bioheat transfer simulation.

1. Introduction

Laser Interstitial Thermo Therapy (LITT) is increasingly being used as a surgical method to destroy cancerous tissues through thermal coagulation and thermal necrosis rather than ablation. LITT treatment is minimally invasive and simple to perform, potentially decreasing complications and minimizing the hospitalization time. Also, this method provides enough dose of heat to the desired site while minimizing damage to surrounding tissues.

Initially, LITT was performed with a simple bare fiber, today different kinds of techniques (single or multiple applicators with simultaneous or subsequent laser application) or diffusing fibers are used to induce a thermal necrosis in the desired small or large volume [1].

The biological effects of laser energy depend on the laser wavelength, laser power, the duration of irradiance, blood perfusion, and both the optical and thermal properties of the tissue involved [2]. Thus, there is a need for treatment monitoring to have precise information about the extent of thermal damage in tissues caused by laser interstitial coagulation.

Modeling laser-tissue interaction is beneficial for the analysis and optimization of the parameters governing planned laser surgical procedures. Nevertheless, we still lack an adequate model that grants accuracy. Most of the suggested models depend greatly on simplifications of the real problem, either in the geometry they offer or in the system of equations they use. Some models, which use the bioheat equation, neglect the role of the changes in the tissue properties during temperature elevation processes, which deem such a model unrealistic, especially considering high temperatures [3]. Some of the proposed models used Mont Carlo simulation [4].

Also, predicting the size and shape of the zone of necrosis before the treatment requires a thermal model to calculate the laser-induced temperature distribution in the tissue and a model for the time–temperature dependence of cell death.

LITT treatment method was used for treating different types of tumor in the liver, head, neck, brain, etc. Another promising application of LITT is the treatment of low risk and low volume prostate cancer [5]. Few modeling methods have simulated the behavior of LITT in prostate tissue.

The aim of this paper is to present a 3D simulation model for calculating the extent of heat and estimating the volume of tissues damaged for prostate cancer animal model. This simulation model was achieved using COMSOL Multiphysics.

2. Materials and Methods

2.1 Animal model

Investigations were conducted in accordance with accepted ethical and human practices, and approved by the local animal care committee at our institution (Ethic Committee in Animal Experimentation of Lille University; agreement number: A59-35010 DHURE; file number: CEEA – 14-2009).

For experiments, we used Dunning R3327-AT2 syngenic prostate adenocarcinoma implanted ($2x10^6$ cells) by subcutaneous injection in the flank of Copenhagen rat 8 weeks of age or older (Harlan Laboratories TM).

Ten rats were used for this study. A latency period of 3 weeks was typically observed to obtain a subcutaneous tumor diameter of 3 cm.

2.2 Laser procedure

The laser used to induce hyperthermia in tissue was a diode laser system emitting at 980 nm. The device was equipped with cylindrical diffusing fiber (CDF) of 10mm length with a 500µm core diameter developed by our team (Diffusing tip optical fiber) [6]. In order to induce local hyperthermia in the subcutaneous tumor, the laser procedure was performed as following: the CDF was inserted into the center of the tumor; the power provided from the source was 5 watt with energy fluence of 1145 J/cm^2. The irradiance duration was 75s.

Using a thermal camera the maximum temperature measured at the tip end of fiber irradiance was 155 C°. Finally, an MR acquisition was performed at t+ 48 hours. The MR images were used to estimate the volume of thermal damage by using the ArtiMED™ platform implemented in U703 laboratory. Figure 1 presents the treated volume.

2.3 Modeling in COMSOL Multiphysics

The heat elevation in prostate tissues and thermal damage was modeled using COMSOL Multiphysics 4.0. In the following sections, we will describe the different stages to construct our model in COMSOL Multiphysics.

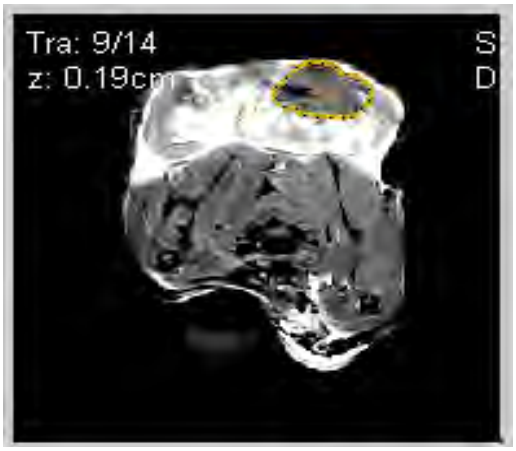

Figure 1. T1 MR Image of the rat with the tumor and the treated area in hyposignal.

2.3.1 Geometrical description of the model

The geometry used to simulate was based on a 3D model consisting of a CDF inserted inside a volume of homogenous tissues. The dimensions of this volume were 70 mm × 70 mm × 20 mm. This volume was surrounded by infinite and homogenous tissues. The dimensions of the CDF were: diameter: 500µm, length: 10.0 mm (figure 2).

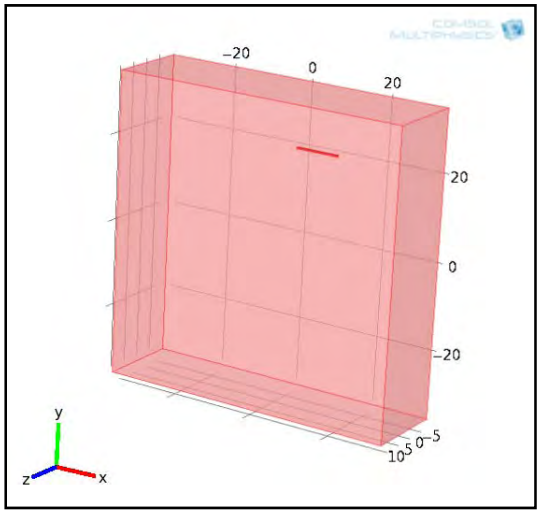

Figure 2. Geometry of the LITT model for Dunning R3327AT-2 rat prostate.

2.3.2 Heat distribution

Interaction heat-tissue during the LITT of prostate was modeled by developing the bio-heat equation in a 3D geometry study. In order to describe the thermal process we used Bioheat Transfer application mode with time dependent (Comsol 4.0).

The governing equation is

$$C_p.\frac{\partial T}{\partial t} - \nabla.(\hbar.\nabla T) = w_b.C_p.[T_b - T] + Q_{met} + Q_{ext}$$

Where T is temperature (°K), $C_p = C * \rho$ is heat capacity ($J.mm^{-3}.°K^{-1}$), ρ is density of tissue ($g.mm^{-3}$), C is specific heat of tissue ($J.g^{-1}.°K^{-1}$), $\hbar$ is thermal conductivity of tissue ($W.mm^{-1}.°K^{-1}$), w_b is blood flow rate ($ml.g^{-1}.min^{-1}$),T_b is the blood temperature, t is time (s), Q_{met} is the metabolic heat source and Q_{ext} is the external heat source.

Values of parameters used in our model for heat calculation were reported in [7] (table 1). Bioheat equation was simplified, considering that metabolic heat and the external heat source are negligible respect to the laser induced heat. The boundary conditions consider the ($T = T_b$) on tissues walls. The initial temperature of tissues was considered T_0=37°C. The thermo-optical parameters were considered constant during the thermal process.

2.3.3 Thermal damage

Thermal damage in cells and tissue can be described mathematically by a first-order thermal-chemical rate equation, in which temperature history determines damage. Damage is considered to be a unimolecular process, where native molecules transform into a denatured/coagulated state through an activated state leading to cell death. Damage is quantified using a single parameter Ω, which ranges on the entire positive real axis and is calculated from the Arrhenius law [7, 8]. Damage Ω is dimensionless, exponentially dependent on temperature, and linearly dependent on time of exposure and is calculated from the Arrhenius law:

$$\Omega(r,\tau) = \ln\left(\frac{C(r,0)}{C(r,\tau)}\right) = A_f \int_0^{\tau} \exp\left(\frac{-E_a}{RT(r,t)}\right) dt$$

where $C(r,0)$, $C(r,\tau)$ are the concentrations of the undamaged molecules at the beginning and at time τ, respectively. $A_f\,(s^{-1})$ is the frequency factor, $E_a\,(J.mole^{-1})$ is the activation energy, R ($J.mole^{-1}.°K^{-1}$) is the universal gas constant. T (°K) is the temperature. Values of parameters used for thermal damage calculation in our model are reported from literature [9] and mentioned in table1.

Damage Ω is a parameter that is reflective of the extent of damage. A is a frequency factor that describes how often a change in configuration actually occurs when such a reaction is energetically possible.

The equation indicates that the measure of damage describes the probability of tissue being destroyed. It is the logarithm of the ratio of the initial concentration of undamaged tissue to the concentration once damage has accumulated, for the time interval t = 0 to t = τ. Therefore, Ω = 1 corresponds to an irreversible damage of 100% of the affected cells.

3. Results

Experimental validation of the model was performed, where the results of the bioheat equation and Arrhenius integral application in our model were compared with results of *in vivo* experiments. The maximum heat diffused in tissues after 75 seconds from the cylindrical diffusing (CDF) fiber modeled in COMSOL Multiphysics was 156.3 C° (Figure 3 and figure 4) versus 155 C° the maximum heat measured at the tip end of plastic optical fiber in the experiment (<1%).

The mean volume of the tissue necrosis, estimated on the t+48 MRI, for the ten rats was 0.98±0.05 cc.

For the simulations on COMSOL volumes were: 1.38 cc when T=44° C, 1.1 cc for T=46°C and 1.00 cc when T=50 C° (Figure 5).
These values are considered in good agreement because the necrosis of tissues occurs when temperature rises up to 44°C.

4. Conclusion

LITT treatment of the prostate is a promising therapy method. It needs further more evaluation and understanding of the heat extent

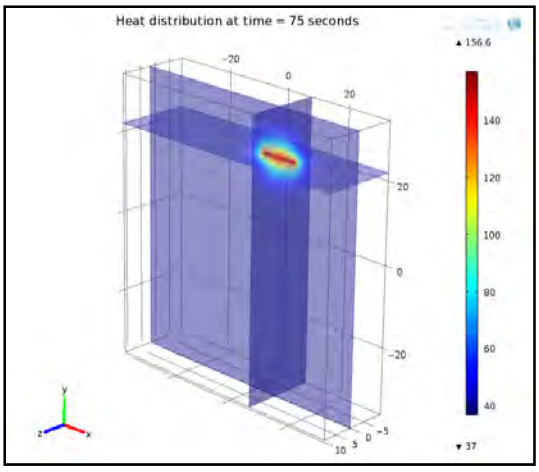

Figure 3. Heat distribution around the cylindrical diffusing fiber (CDF) after 75s of laser diffusion.

in tissues to be a surgical method applied in the routine hospitalization.

In this paper we presented a numerical simulation model of LITT treatment method for the Dunning R3327AT-2 rat prostate and validated these simulations with *in-vivo* experimental results. A laser diode system attached to a cylindrical diffusing fiber (CDF) was used to diffuse laser at 980 nm wavelength at power = 5 w during 75 seconds in tissues.

This approach has enabled greater understanding of global impact of LITT method through the calculation of heat distribution and the thermal damage. Post-laser thermotherapy tissue injury has been quantified by calculating the thermal damage (Ω).

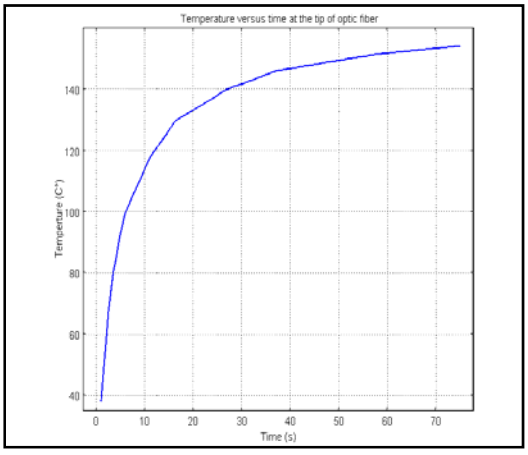

Figure 4. Heat rising in time.

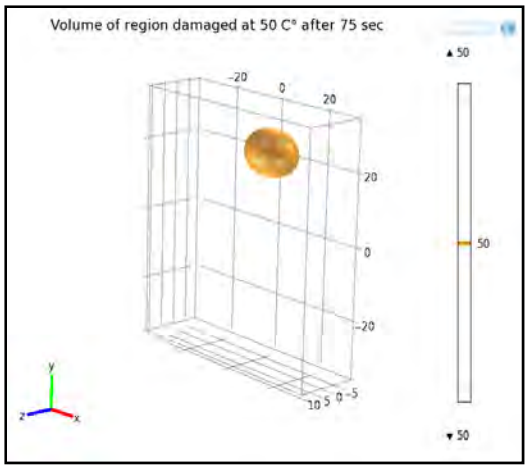

Figure 5. Tissue volume that has reached at 50C°

The threshold of irreversible cellular injury where Ω=1 corresponding to a temperature of 50°C.

6. References

1. B. Algermissen, C.M. Philipp, U. Müller, P. Urban, H.P. Berlien, Interstitial Thermotherapy (ITT) using Nd:YAG Laser as a new option for the treatment of Neuroma, *Med. Laser Appl*. **16**: 129–134 (2001).
2. Y. Mohammed, J.F. Verhey, A finite element method model to simulate laser interstitial thermo therapy in anatomical inhomogeneous regions. *Biomed Eng Online*, **4**(1):2 (2005).
3. I. Chang, Finite Element Analysis of Hepatic Radiofrequency Ablation Probes using Temperature-Dependent Electrical Conductivity, *Biomed Eng Online*, **2**(1):12 (2003).
4. S. C. Jiang, X. X. Zhang, Effects of dynamic changes of tissue properties during laser-induced interstitial thermotherapy (LITT), *Lasers in Medical Science*, **19**: 197–202 (2005).
5. G. Müller, A. Roggan, Laser-induced interstitial thermotherapy. *SPIE Optical Engineering Press*, Bellingham, 83–189 (1995).
6. P. Rochon, R. Viard, et *al.*. Hepatic tumors necrosis using optical diffusing fiber and thermoregulation, *Lasers Surg Med*, 40(**S20**): 69 (2008).

7. J.C. Bischof, D. Smith, P.V. Pazhayannur, C. Manivel, J. Hulbert, and K.P. Roberts, Cryosurgery of Dunning AT-1 Rat Prostate Tumor: Thermal, Biophysical, and Viability Response at the Cellular and Tissue Level, *Cryobiology*, **34**:42–69 (1997).
8. J. Jankun, R.W. Keck, E. Skrzypczak-Jankun, L. Lilge and S.H. Selman, Diverse optical characteristic of the prostate and light delivery system: implications for computer modeling of prostatic photodynamic therapy, BJU International, **95**:1237 – 1244 (2005).
9. M. Niemz: Laser-Tissue Interactions, Fundamentals and Applications. 1st edition. Springer-Verlag Berlin Heidelberg (1996).
10. H.E. Xiaoming, W.F. Wolkers, J.H. Crowe, D.J. Swanlund and J.C. Biscof, In Situ Thermal Denaturation of Proteins in Dunning AT-1 Prostate Cancer Cells: Implication for Hyperthermic Cell Injury, *Biomedical Engineering*, **32** (10) : 1384 – 1398 (2004).

7. Appendix

Table 1: Physical parameters of the AT-1 Dunning rat prostate used in numerical simulation

$\lambda = 980\ nm$	Parameters	Values
Thermal coefficients	C $(\mathrm{J.g^{-1}.^{\circ}K^{-1}})$	4.20
	ρ $(\mathrm{g}.mm^{-3})$	0.999×10^{-3}
	$\hbar$ $(W.mm^{-1}.^{\circ}K^{-1})$	5.52×10^{-4}
	w_b $(ml.\mathrm{g^{-1}}.min^{-1})$	0.10
Tissue Damage Coefficients	$\mathrm{A_f}$ $(\mathrm{s^{-1}})$	7.60×10^{66}
	$\mathrm{E_a}$ $(\mathrm{J.mole^{-1}})$	4.30×10^{5}
	R $(J.mole^{-1}.^{\circ}K^{-1})$	3.41847