A PRELIMINARY STUDY OF THE TRANSPUPILLARY THERMOTHERAPY EFFECTS IN OCULAR TUMORS USING THE FINITE VOLUME METHOD WITH UNSTRUCTURED MESHES

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Abstract. *This paper presents a two-dimensional numerical model for the human eye in order to investigate the transient temperature evolution and the associated thermal damage in various regions of the human eye. We pretend to monitor the ablation front evolution. The patient has a choroidal melanoma and he is submitted to a laser radiation. To determine the temperature field, a model was developed by employing the Pennes Bioheat Transfer Equation (BHTE), that includes a source/sink term which takes into account the heat transferred due to the blood perfusion. The Birngruber model was used to determine the damage function during the laser transpupillary thermotherapy. This model describes the heating effect on the rate of a chemical reaction, and considers the variation in concentration of undamaged molecules, using the Arrhenius law. The analysis was done using an ultrasound image of the patient. This kind of exam provides the eye and tumor dimensions. The CFD (Computational Fluid Dynamics) commercial software, FLUENT, which employ the finite volume method (FVM), is assigned to be the solver of model. The numerical results show satisfactory values and they are qualitatively consistent with the available literature. The strengths of the model are: the use of a single scalar term which accounts for the blood perfusion; the absorption probability of ocular tissue is modulated based on the Lambert-Beer's law to reproduce the exponential attenuation of the laser light with the depth within a biomaterial; the tissue thermal properties for each eye region are homogeneous and isotropic. In the future, these results will be used to analyze the propagation of the tumor ablation front, with the consequent change in its shape and dimensions. Then, these information will be able to guide the physician about planning the whole procedure.*

Keywords*: Choroidal Melanoma, Transpupillary Thermotherapy (TTT), Bioheat Tranfer, Finite Volume Method, Unstructured Meshes.*

1. INTRODUCTION

The choroidal melanoma is the most common eye cancer, with an incidence of about 6 cases per 1 million population per year (Cruickshanks et al., 1999). It affects preferably individuals above 50 years old and Caucasian, but is uncommon in black and Asian races. In some patients it is asymptomatic, while in others it can cause loss of vision, defects in visual field, photopsia or pain (Arcieri et al., 2002).

The choice of treatment for choroidal melanoma is controversial in many respects and there is no consensus on the protocol to be followed. Among the different therapeutic options it can be mentioned: periodic observation, enucleation, exenteration, localized surgical resection, brachytherapy, irradiation by external beam of charged particles, photocoagulation, and transpupillary laser thermotherapy (Valenzuela, 2009). The tumor removal through surgery is a painful, traumatic and sometimes not effective. Therefore, the hyperthermic treatment called laser transpupillary thermotherapy has aroused great interest showing satisfactory results for certain types of tumors.

The transpupillary thermotherapy (TTT) is a treatment modality that uses a modified diode laser with a wavelength of 810 nm to produce a local and uniform heating with a subsequent obliteration of malformed vessels and reduction in the tumor size (Shields et al., 1998). The TTT is a recent method that has proved effective in treating small melanomas into the posterior choroid, due to irregular vascular system that prevents a good spread of heat, warming the tumor more than peritumoral tissues.

The laser application time is a function of its power, being determined experimentally by the own tissue reaction. That is, when the laser application begins, there is a slight change in color from melanoma. The treatment is interrupted at this point (Roizenblatt et al., 2002). This procedure is unsatisfactory because it can lead to mistakes by the doctors who conduct the procedure. Therefore, the numerical simulation of these procedures can be critical, providing reliable parameters such as exposure time to conduct the surgery with minimal risk to the patient.

To make the simulation of the temperature field and the thermal damage function an ultrasound image of a patient with a choroidal melanoma was used. As the domain to be simulated involves complex geometries it was used unstructured meshes with triangular elements. The commercial software FLUENT was used to solve the Bioheat Transfer Equation in its two-dimensional form, in transient and steady state regimes. FLUENT solves the equations based on finite volume method which ensures local and global conservation of the analyzed property.

2. OBJECTIVES

To develop a mathematical and computational model to determine the temperature, in transient and steady state regimes, and their effects in the human eye when submitted to the radiation of a laser. Later, this model will also be used to evaluate the thermal damage caused to the tissue, and to provide an estimate of the optimal time of laser exposure in procedures of TTT.

3. DESCRIPTION OF THE PHYSICAL MODEL

The first quantitative relationship that describes the heat transfer in human tissues and considers the effects of the blood perfusion in the tissue temperature was presented by Harry H. Pennes (Charny, 1992). It represents the spatial and temporal temperature distribution in living tissues, and is denominated "bioheat transfer equation (BHTE)", or it could also be called "Traditional" or "Classic" or "Pennes" bioheat equation. Due to its simplicity, this is the most widely used thermal model for living tissues. The bioheat transfer equation is a heat transport equation that includes a source/sink term that accounts for the heat transferred through the blood perfusion. The general statement is

$$\rho_t c_t \frac{\partial T_t}{\partial t} = \nabla(k_t \nabla T_t) + Q_m + Q_P + Q \tag{1}$$

where, $\boldsymbol{c}$ is the tissue specific heat (J/kg K); $\boldsymbol{\rho}$ is the tissue density (kg/m^3); $\boldsymbol{T}$ is the tissue temperature (K); $\boldsymbol{t}$ is time (s); $\boldsymbol{Q_m}$ is the metabolic heat generation rate (W/m^3); $\boldsymbol{Q_P}$ is the sink/source term which accounts for the heat transferred from blood perfusion (W/m^3); $\boldsymbol{k}$ is the tissue thermal conductivity (W/m K); $\boldsymbol{Q}$ is the heat source due to external laser irradiation (W/ m^3); the subscript '*t*' stands for tissue.

The second term on the right side of Eq. (1) represents a heat sink that is due to convective removal of heat carried by the blood through the capillary vasculature that is present in living tissues. The term is represented by (Diller, 1982 in: Smith, 2004):

$$Q_P = \omega \rho_b c_b (T_a - T_v) \tag{2}$$

where, $\boldsymbol{\omega}$ is the rate of blood perfusion (s^{-1}); $\boldsymbol{\rho}$ is the blood density (kg/m^3); $\boldsymbol{c}$ is the specific heat (J/kg K);$\boldsymbol{T}$ is the temperature (K). The subscripts '*b*', '*a*' and '*v*' stands for blood, the arterial blood entering the tissue and the venous blood leaving the tissue, respectively.

Usually it is assumed that the temperature of blood entering the capillary region is equal to the temperature of arterial blood (T_b=T_a), and the temperature of the blood that leaves is equal to the temperature of venous blood, T_v, and can be considered equal to the local tissue temperature (T_v=T_t). The blood velocity in the capillaries is very small, with a Peclet number (which expresses the ratio of heat transfer by convection and heat transfer by conduction) much smaller than unity. This justifies the consideration that the temperature of venous blood leaving the tissue is equal to the temperature of the tissue (Charny, 1992 in: Silva, 2004). Then Eq. (1) becomes:

$$\rho_t c_t \frac{\partial T_t}{\partial t} = \nabla(k_t \nabla T_t) + \omega \rho_b c_b (T_a - T_t) + Q \tag{3}$$

For this study, the external source term Q, in Eq. (3), is due to the infrared radiation induced by a diode laser with a wavelength equal to 810 nm and a continuous wave.

Figure 1 shows a simplified schematic representation of a patient eye, with melanoma, as a structure composed of layers of different ocular tissues. To simplify the modeling, the following hypotheses were assumed:

a) the human eye is a solid structure composed of layers of different tissues and in contact with each other;
b) the incident beam of laser radiation is considered with the standard "spot", whose intensity I_0 is constant and independent of *r (radius of the laser image);*
c) the radiation penetrates into the tissue without scattering;
d) the thermal properties for different types of tissue are isotropic and homogeneous;
e) the corneal surface exchanges heat by convection and radiation with the external environment;
f) the metabolic heat generation is not considered, because its value is much lower than the laser power;

g) the blood temperature is considered equal to 37 degrees Celsius;
h) the retina and the tumor are considered as one region due to the small thickness of the retina and the fact that most of the infrared radiation is absorbed into the melanotic tumor tissue.

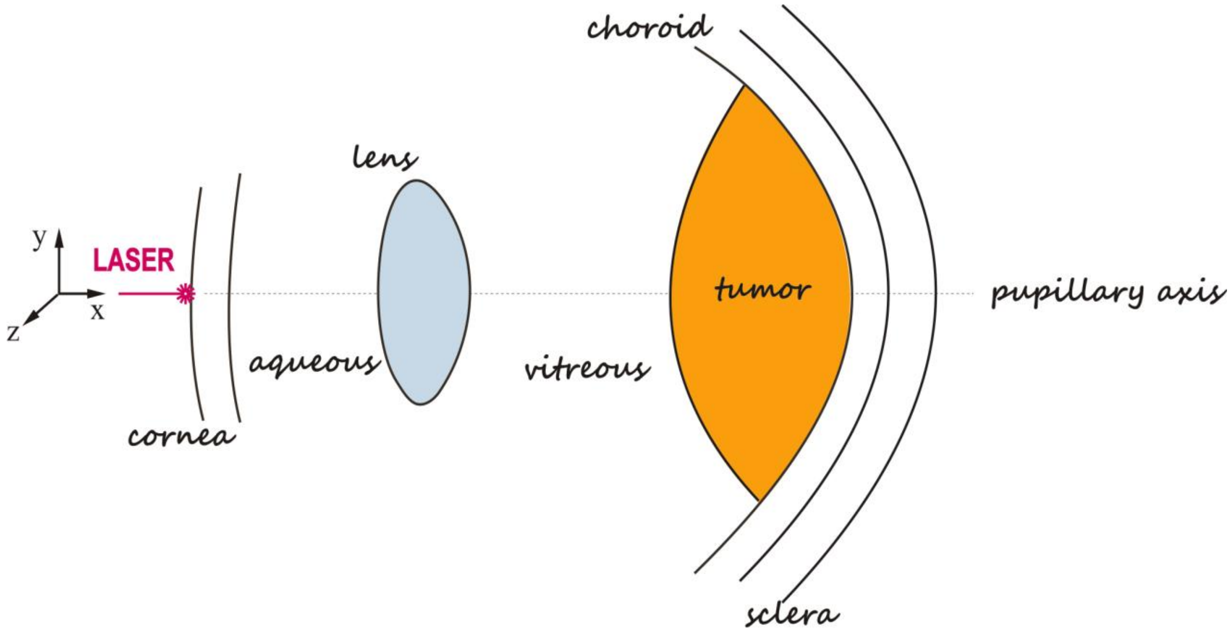

Figure 1. Simplified schematic representation of tissues for modeling the eye

One of the most important terms in Eq. (3) is the source term *Q*. As a first approximation, one can assume that the laser light penetrates the tissue without scattering and the absorption local rate of the radiant energy is proportional to intensity, according to Beer's law (Shitzer, 1985). This leads to an exponential decrease in intensity and absorption rate along the propagation direction of a cylindrical beam passing through a homogeneous medium. The volumetric rate of heat generation due to the laser source, *Q(r, z)* in Eq. (3) is thus given by (Welch, 1985)

$$Q(r,z) = \beta I_0(r)e^{-\beta z} \tag{4}$$

where, r is the radial position within the cylindrical beam (m), z is the distance between the surface where the incident radiation reaches and the absorbing layer (m); I_0 is the beam intensity on the absorbing layer surface (W/m^2) and, β is the absorption coefficient (m^{-1}).

Equation (1) can be written in a more appropriate way to describe the formulation of the finite volume method in the integral form as:

$$\int_V \rho c \frac{\partial T}{\partial t} dV = \int_V \frac{\partial q_j}{\partial x_j} dV + \int_V S dV \tag{5}$$

where, q_j is the heat flux in the x_j direction; S represents the heat source/sink terms, due to the heat deposited by laser radiation and the heat removed by blood perfusion, ie, the sum of Eq.(2) and Eq.(4). The spatial domain of the problem is represented by V, with x_j being the independent space variable, and j ranging from one to the number of spatial dimensions.

Applying the divergence theorem, the previous equation can be written as:

$$\int_V \rho c \frac{\partial T}{\partial t} dV = \oint_\Gamma q_j n_j d\Gamma + \int_V S dV \tag{6}$$

where, V represents an arbitrary control volume, with the contour, Γ, closed.

The thermal damage in living tissues is defined as the protein denaturation or the loss of the biological functions of the molecules found in the cells or in the fluid among the cells, due to the heating induced by the laser. A critical condition related with the temperature can be defined above that irreversible damage will happen (Routh, 1971).

Birngruber (in: List et al., 2000) developed a model to determine the damage function in the retina and in the choroid during treatments with transpupillar laser thermotherapy. The model describes the effect of the heat in the chemical reaction rate and, it considers the variation in the undamaged molecules concentration, using the Arrhenius's law. The general form of the Arrhenius's integral is:

$$\Omega = C \int_{0}^{\tau_{denat}} T(t) \exp\left[-\frac{\Delta E_{at}}{RT(t)} \right] dt \tag{7}$$

where, $\boldsymbol{C}$ is a pre-exponential constant ($C=6.81 \times 10^{41}\ s^{-1}$); $\boldsymbol{\Delta E_{at}}$ is the activation energy for the denaturation process; $\boldsymbol{R}$ is the gases universal constant ($R=8,31\ J/mol\ K$) and $\boldsymbol{\tau_{denat}}$ is the denaturation time.

4. TWO-DIMENSIONAL ANALYSIS OF THE PROBLEM

4.1. The problem analyzed

This study will be considered a two-dimensional model of the human eye to determine the temperature and the thermal damage inside the eye of a patient with a choroidal melanoma. The analysis will be made from an ultrasound image of a patient, in which exists information about the dimensions of the eye and the tumor.

In addition to the hypotheses described in previous section the following assumptions and considerations are adopted for the simulation of the problem considered here:

a) The ciliary body is the vascular structure that secretes the transparent liquid - aqueous humor - in the eye and contains the ciliary muscle, responsible for changing the shape of the lens. The thermophysical properties of iris and ciliary body are identical to the aqueous humor (Amara, 1995). So these regions will be treated as only one homogeneous region;
b) Being a very thin layer and also due to the fact that the tumor absorbs the largest percentage of the laser energy, due to the high concentration of melanin present in the same the retina and the tumor will be treated as only one single homogeneous region;
c) The aqueous humor is considered stagnant (Emery et al., 1975; Scott, 1988; Kramer et al., 1978);
d) The heat transfer within the eye occurs by conduction;
e) Blood perfusion is considered to exists only in tumor and choroid;
f) The focused action of the lens is neglected because the diameter of the laser beam is very small and strikes the cornea in a direction that coincides with the pupillary axis.

4.2. Eye geometry and properties

Figure 2 shows a picture of the human eye with a choroidal melanoma, constructed from an ultrasound image, divided into seven regions for the modeling purposes. The eye diameter along the pupillary axis is approximately 2.4 cm (Adler, FH, 1970; L'Huillier, JP & Apiou-Sbirlea, G., 2000 in: Narasimhan et al., 2009). The posterior half of the human eyeball is nearly spherical (Forrester et al., 2001). Each region is considered homogeneous and the eye can be considered symmetric with respect to the pupillary axis since the presence of the optic nerve was disregard.

The cornea is the front surface of the eye, whose thickness is assumed constant and equal to 0.4 mm. The lens of the human eye has a diameter of 8.4 mm and a thickness of 4.3 mm. The thickness of the sclera is constant and approximately equal to 0.7 mm. The diameter and thickness of the tumor are, respectively, equal to 14.2 mm and 7.9 mm.

It is assumed that the values of thermal conductivity (k), density (ρ), specific heat (c), blood perfusion (ω) and absorption coefficient (β) are constant within each region of the eyeball. These properties can be found in the literature and are described in Table 1.

The greatest difficulty in accurate modeling for heating in cancer cells stems from the lack of information and reliability on the volumetric rates of blood perfusion, especially in neoplasic tissues. In tumors, this fact becomes even more complex, because the tumor grows in a disorganized way and the value of perfusion rate can't be regarded accurately, increasing the imprecision in the calculated temperature values. Moreover, the value and direction of blood flow in tumors are not fixed due to the growth process and due to vascular necrosis. And yet, the capillary venous can behave as a capillary blood at different times (Jain, 1985).

Table 1. Thermophysical properties (S.I. system) for the layers of the eye and the tumor

Layer	*Density*	*Specific heat*	*Thermal conductivity*	*Absorption coefficient* (*)
Vitreous	1000	4178	0.603	7.69
Tumor	1040	3900	0.70	1250.00
Sclera	1050	4178	0.58	120.52
Cornea	1050	4178	0.58	120.52
Aqueous	1000	3997	0.58	16.82
Lens	1050	3000	0.40	20.26
Choroid	1000	4190	0.628	6868.33

(Sources: Amara, 1985; Scott, J.A, 1988; Guimarães, C., 2003 and Özen, Ş., 2002)

(*) The values for the absorption coefficient in the different layers of the eye for infrared diode laser (810 nm) were obtained by linear interpolation using the data found in Amara (1995) that provides the coefficient values for the Nd-YAG laser (1060 nm) and for the Ruby laser (694.3 nm).

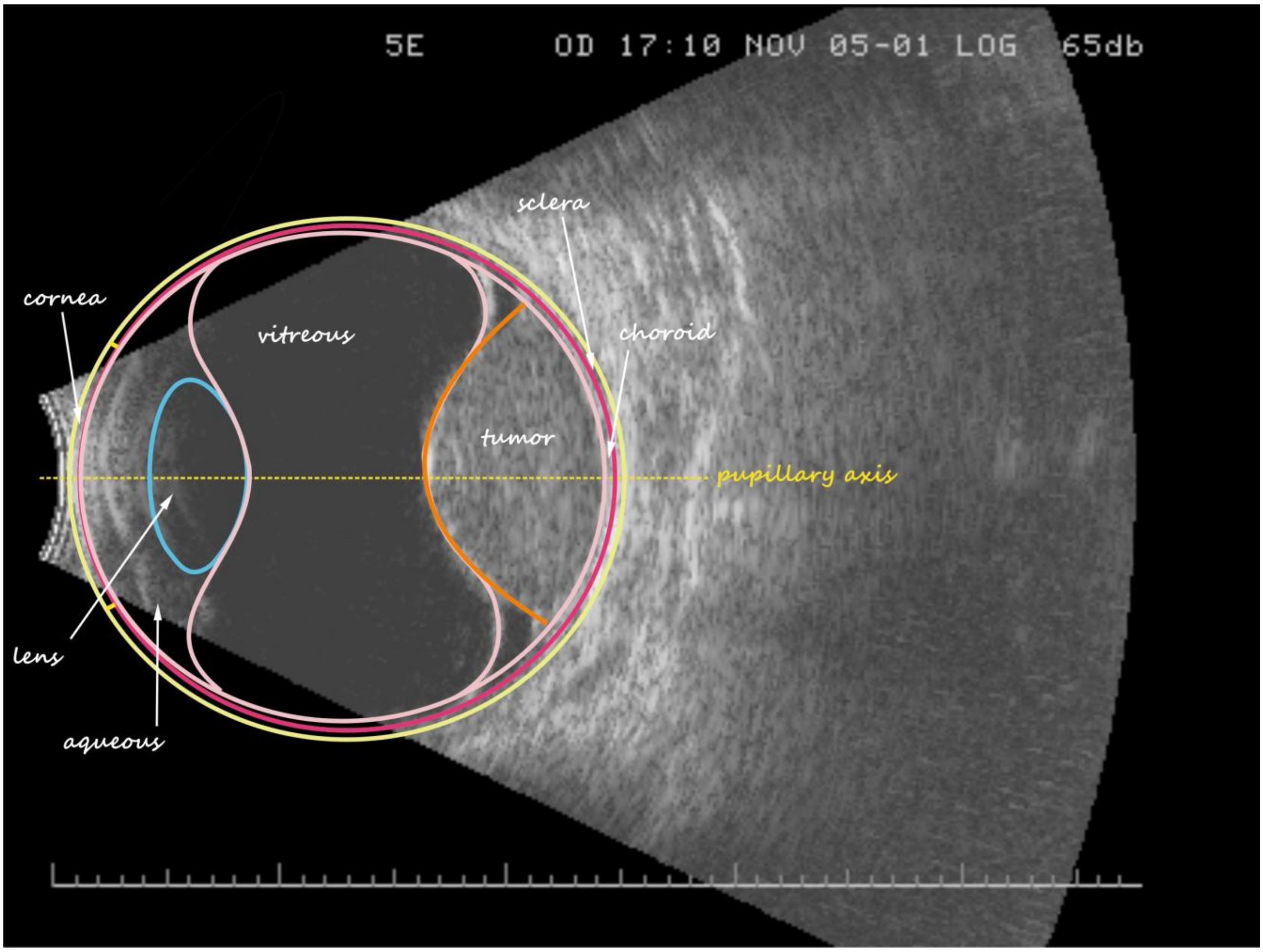

Figure 2. A scheme for the eye model with a real choroidal melanoma

4.3. Initial and boundary conditions

a) On the back surface of the sclera a boundary condition of constant temperature at 37 ºC was considered, that is the average temperature of human beings body core.
b) It is considered that the cornea is the only region of the eye exposed to the environment. When the room temperature is lower than the temperature of the surface of the cornea, the eye loses heat by convection, radiation and evaporation of the tear film. A layer of tear film covers the surface of the cornea. This layer evaporates and is constantly replenished by blinking of the eyelids. This heat lost by the cornea generates a heat flow in regions of higher temperatures inside the eye to the corneal surface. Then, a convective boundary condition with

heat transfer coefficient estimated by Lagendijk (in: Scott, 1988) considering the evaporation of the tear film and heat exchange by radiation and convection of the cornea to the environment is: h = (20 ± 2) W/m^2 ºC.

c) The initial temperatures in different regions of the eye, are obtained through a preliminary simulation of the steady state regime of the eye not exposed to any radiation and with a starting temperature equal to 37 ºC.

4.4. Numerical method and grid convergence

With the considerations outlined in the previous sections a preliminary case was set in order to calculate the temperatures and thermal damage function at all points of the domain.

Unstructured meshes were adopted as they are flexible to real with complex geometries, allowing local refinement in specific regions.

The adopted meshes have been created using the commercial software GAMBIT. The coordinates of the image, used by the GAMBIT mesh generator, were acquired through a computer program APID – Acquire Points in Digital Images - (Santos, 2007). Triangular elements were used in the mesh with refinement (higher amount of elements) in the tumor region, where the largest and most rapid temperature changes are expected. The FLUENT commercial software (http//www.ansys.com) is assigned as the solver of the discretized models. The calculations were performed using an implicit second order upwind scheme.

A grid convergence study has been carried out for the eye with laser irradiation. During transient regime, a laser intensity of 70,736 W/m^2, a beam diameter of 3 mm for the laser, a body temperature of 37 ºC and, an ambient temperature of 25 ºC were imposed. The results of this study are shown in Fig. 3. The case with 104,186 cells was considered the nearest of the real solution. The maximum difference between the results obtained with this mesh and the results obtained with a mesh of 11,702 cells was 0.137%. Based on these results, the mesh with 11,702 cells was chosen for the other simulations.

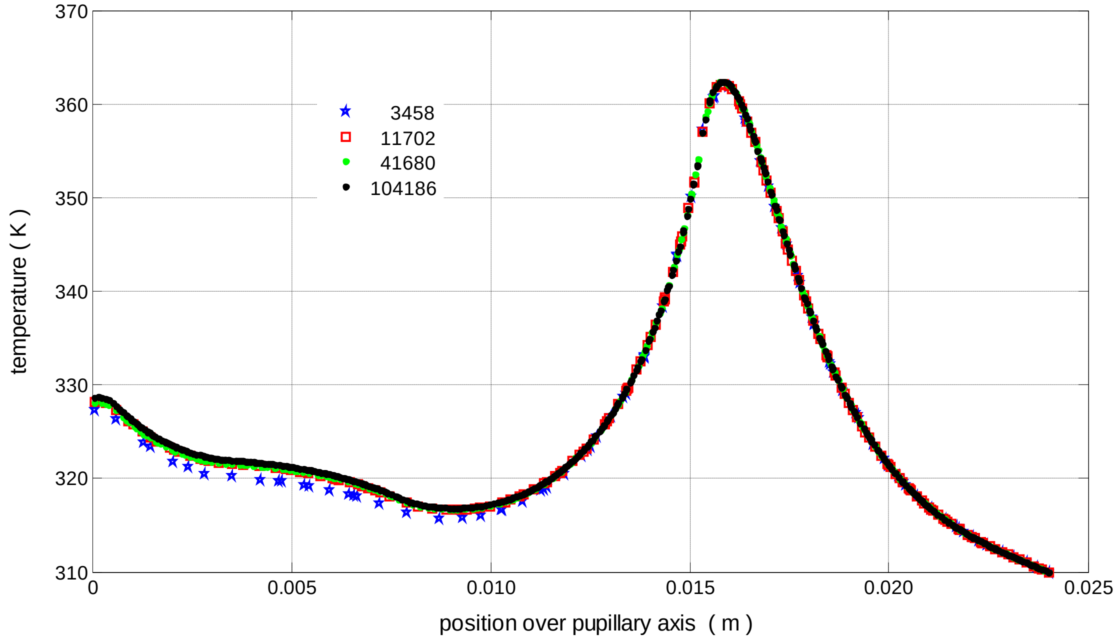

Figure 3. Temperature distribution at the pupillary axis after one minute of laser aplication. The calculations were executed using meshes of 3458, 11702, 41680 and 104186 cells

4.5. Results

Initially we analyze the heat transfer in the human eye without laser radiation. Steady-state temperatures were calculated over the entire domain of the eye. This result will be used as the initial values for calculations in transient regime.

Figure 4 shows the field of temperatures obtained for the human eye, with a choroidal melanoma and, not exposed to any radiation. It can be observed that the temperature fields have a circular shape whose radius of curvature decreases as it approaches the cornea. This behavior has to do with the geometry of the eye and the boundary conditions imposed. The cornea covers the front area with an approximate diameter of 10 mm and loses heat to the environment, while the sclera covers the entire surface of the eyeball except the one that corresponds to the cornea, and a constant temperature on the surface. Temperatures range from 34.3 ºC on the outer surface of the cornea to 37 ºC on the outer surface of the sclera.

It is observed that the temperature increases through the cornea, aqueous humor and lens and then tends slowly to the level of 310 K as it passes through the vitreous humor to reach the sclera. This temperature distribution shows a similar behavior to that observed in the results obtained by Amara (1995).

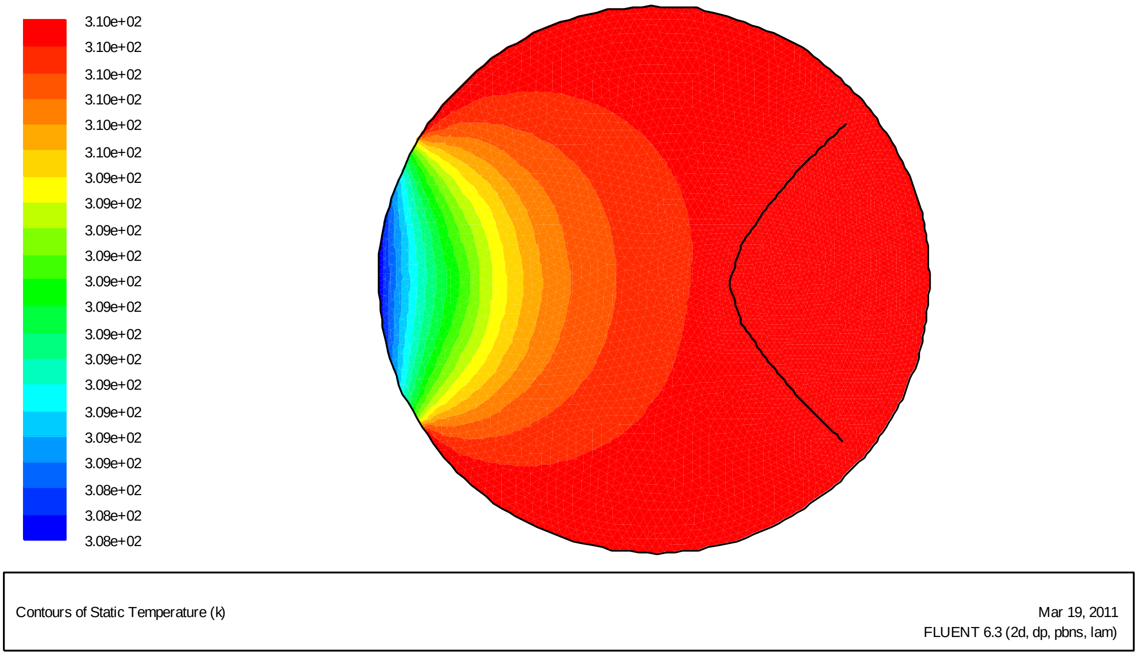

Figure 4. Field of temperatures inside the human eye not exposed to radiation

The field of temperature for the eye irradiated with the laser source is shown in Fig. 5. Unlike the Fig. 4, here the temperature distribution follows another pattern. There are a big difference between this temperature distribution profile and the profile showed in Fig. 4. This difference is due to the laser radiation. Moreover, as the absorption coefficient of the tumor to radiation is higher than in other layers, the temperatures reach the highest values in this region.

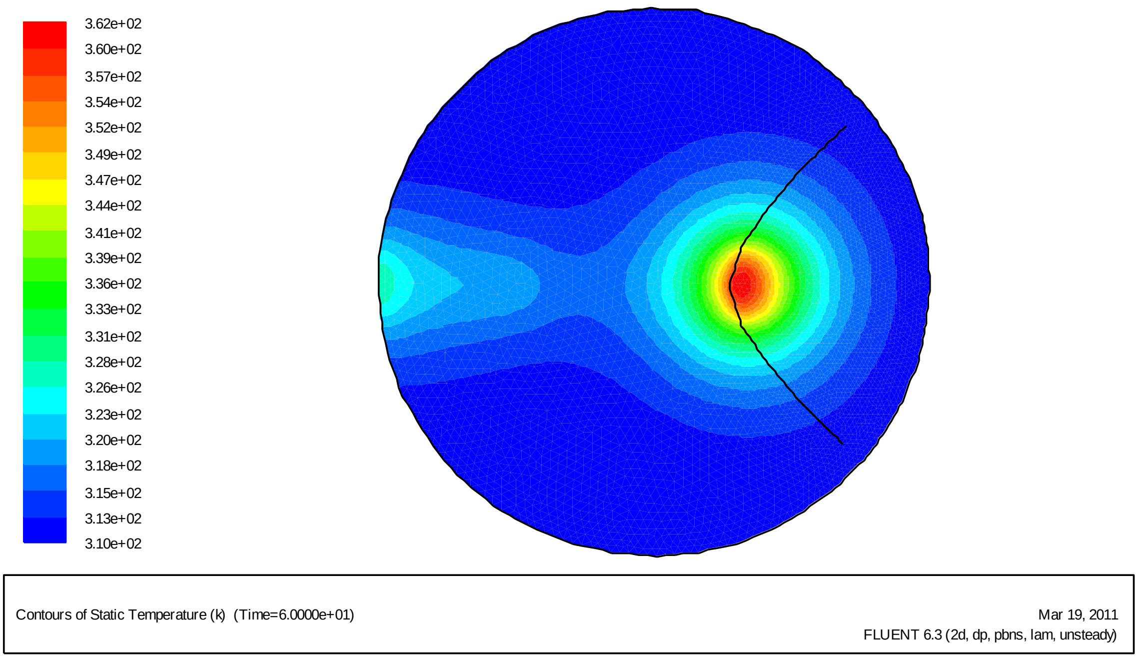

Figure 5. The field of temperatures inside the human eye when irradiated with a laser of intensity 70,736 W/m^2 and an exposure time of sixty seconds

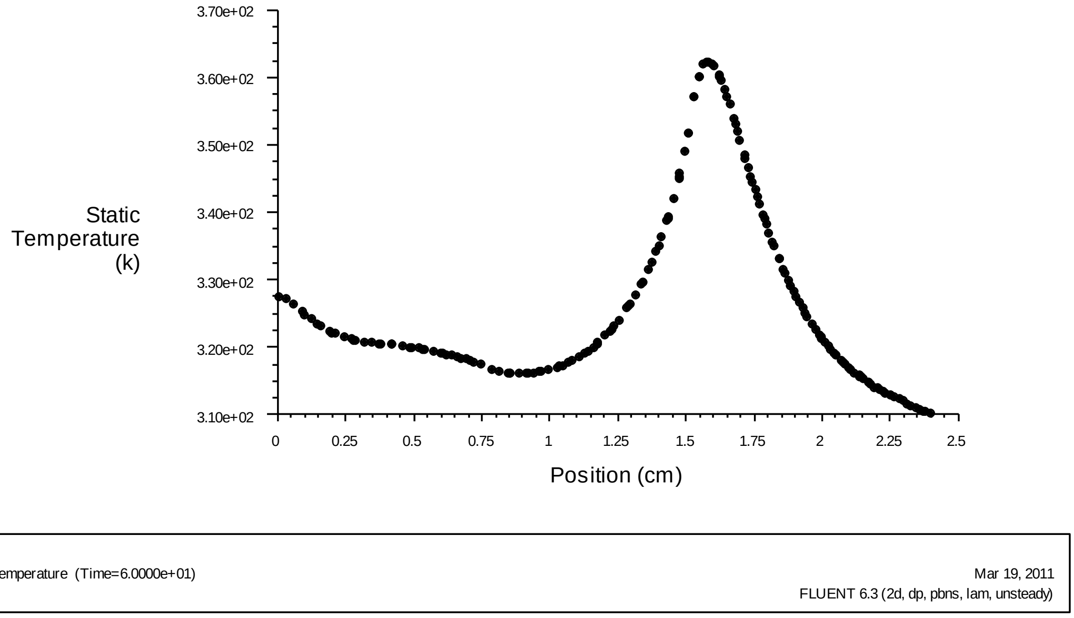

Figure 6. Temperature, after sixty seconds at transient state, along pupillary axis for the eye irradiated with laser of intensity 70,736 W/m^2

In Figure 6, we observe that the highest temperature is located within the melanoma, near its surface. Small changes in temperature at the base of the tumor (≈ 2.2 cm) are consistent with the literature (Journée-de Korver, 1997), which states that reduction in this region is not effective. Therefore, there aren't satisfactory hyperthermic effects in this region. Note also that due to the presence of the tumor and its absorption coefficient, this region becomes warmer than the others; this fact is also in agreement with the literature.

Figure 7 shows the thermal damage as a function of time caused by the laser of intensity 56,588 W/m^2 with two different diameters of the laser beam. An analysis of this graph reveals that for the beam diameter, or image, of 3 mm, the value of damage is about 5 times higher than that for laser radiation with image of 2 mm. It is also evident that the value of the damage continues to increase for a few seconds after turning off the laser (at t = 60 s) and then stabilize at a constant value.

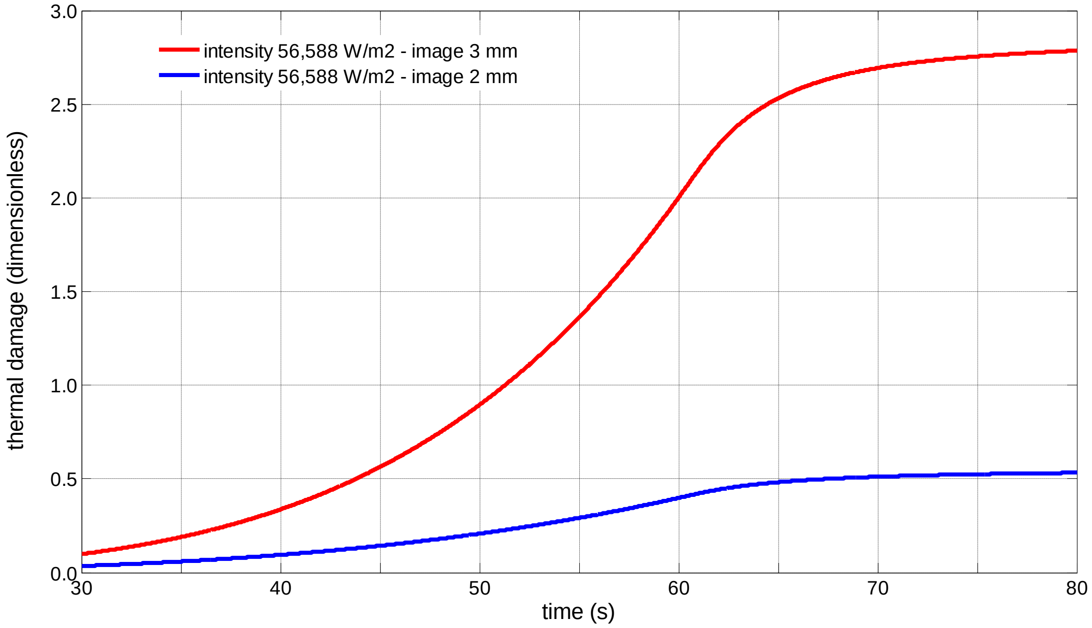

Figure 7. Comparison between damages

Figure 8 represents the total damage versus distance over the pupillary axis for laser radiation of intensity 56,588 and 70,736 W/m^2 with images of 2 and 3 mm. It shows that the radiation passes through the several layers of the eye without causing damage to tissues due to the small coefficient of absorption of radiation in the intraocular medium, except for a small portion of the vitreous humor. It also shows that the value and depth of the damage depends on the intensity and the laser image. Irreversible thermal damage occurs in the melanoma, when the damage function reaches the value of one. The damage reaches a depth of 2.7 mm within the melanoma for a laser of intensity 56,588 W/m^2 and image of 2 mm. For the same intensity, but with the image of 3 mm, the damage extends to a depth of 3.2 mm. When using a laser of 70,736 W/m^2 with the image of 3 mm, the damage reaches a depth of 3.9 mm.

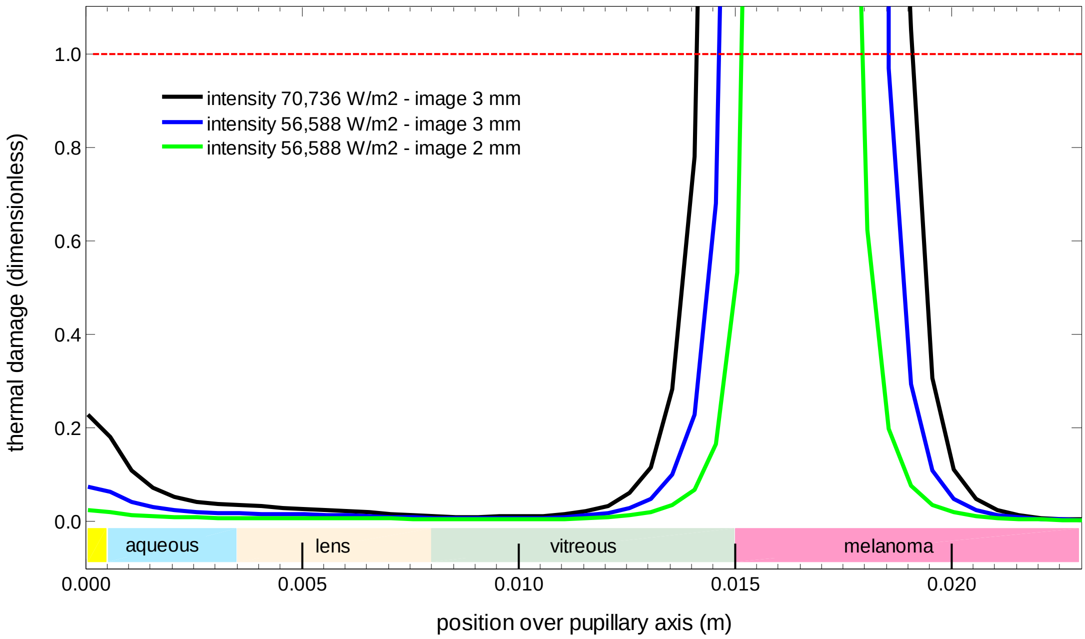

Figure 8. Extension of thermal damage in ocular tissue

4.6. Discussion and Conclusions

First of all, the numerical results obtained by this simulation were considered satisfactory. This technique has been well validated for dealing with problems of similar nature in previous studies (Guimarães, 2003 and Silva, 2004). At this stage, it is necessary to improve the model in terms of the geometric pattern to be used and, in terms of laser application in a higher amount of points. It is also necessary to obtain more accurate physical parameters. The intensity and duration of laser application will be further analyzed. Absorption coefficients of radiation in various types of ocular tissue need to be incorporated in the model. Next we plan to implement in FLUENT, C language, a UDF (User Defined Functions) to calculate the thermal damage in several ocular tissues. With these issues resolved, the analysis of a moving boundary problem will be attempt. This analysis will describe the temporal behavior of tumor destruction while the laser is being applied and, the tumor is being destroyed. With the actual tumor destruction well modeled and the moving front analyzed we expect a larger temperature variation at the tumor back.

Based on that, we consider that it's possible to determine in advance the optimum time in tissue exposure to laser radiation, besides other important parameters such as the intensity and image of the laser to cause a specific injury with a certain depth within the tumor. It should be noted that a small portion of the vitreous humor reaches high temperatures, causing unwanted damage in this tissue. Possibly, this effect is due to the fact that, in this simulation, the regions are considered solid, static and without deformation. However, this can be avoided. Just note that for the lowest laser intensity, the point where the thermal damage starts moves to a position closer to the surface of the tumor, but with an undesired fact that lower depth is reached by the damage within the melanoma. To bring more realism to the simulation, an analysis is being developed for the moving front, which describe the temporal behavior of tumor destruction as the laser is being applied and the tumor destroyed.

Finally, a quick analysis of the simulated domain shows that for this analyzed patient there was a reasonable symmetry of the model with respect to the pupillary axis. For this reason and to avoid a three-dimensional modeling and, the computational costs associated, it can be developed or used an appropriate formulation of the FVM to deal with axisymmetric models. In this formulation only half of the plane containing the axis of the solid of revolution is discretized in order to obtain results much close to reality than a simple 2-D model as considered in this work.

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