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Laser Interstitial Thermotherapy for pancreatic tumor ablation: theoretical model and experimental validation

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Abstract- **This study aims to develop and verify a theoretical model to reproduce the thermal response of pancreatic tissue undergone Laser Induced Interstitial Thermotherapy (LITT).**

The model provides the evaluation of: a) ablated volumes induced by thermal ablation; b) tissue response time to irradiation; and c) heat extinction time. Theoretical volume values were compared with *ex vivo* healthy tissue and *in vivo* healthy and neoplastic tissue volume values. The theoretical model takes into account the differences between healthy and neoplastic tissue due to blood perfusion.

Mathematical model shows that ablated volume of *ex vivo* healthy tissue is greater than *in vivo* one after the same treatment. Moreover, ablated neoplastic *in vivo* tissue volume is greater than healthy *in vivo* one, because of tumour angiogenesis.

Ablated volume values were compared with experimental data obtained by laser treatment of 30 *ex vivo* porcine pancreases. Experimental ablated volume values show a good agreement with theoretical values, with an estimated increase of 61% when power increases from 3 W to 6 W, versus 46% of experimental data, and an estimated increase of 14% from 6 W to 10 W, versus 21% of experimental values. LITT could be an alternative or a neo-adjuvant treatment to surgical resection for pancreas cancer removal, and the proposed model could be the basis to supervising the evolution of ablated volumes during tumor treatment.

I. Introduction

PANCREATIC cancer is the third most common gastrointestinal malignancy and the fourth cause of death in United States [1]. This disease has an extremely poor prognosis, and the average survival for unresectable pancreatic cancer is about 4-6 months. Nowadays, the common surgical procedure for patients with pancreatic head cancer is duodeno-pancreatectomy [2].

An alternative surgical technique for tumors removal is Laser Interstitial Thermal Therapy (LITT), which is a minimally invasive surgical technique applied to destroy neoplastic tissues by thermal coagulation and necrosis, induced by photo-thermal interaction between laser radiation and biological tissue. It was firstly described by Bown in 1983 and it is nowadays routinely used for treatment of liver, prostate, lung, neck, breast and brain tumors. LITT requires laser energy carried inside the deep seated lesion volume through a light guide, e.g. a bare-tip optical fiber [3]. The fiber can be guided in the neoplastic volume by several imaging modality.

Endoscopic Ultra-Sound (EUS) is one of the methods utilized for the diagnosis and staging of pancreatic cancer [4]. With EUS it is possible to guide an optical fiber inside the neoplastic tissue with the use of an echo-endoscope, allowing the entry of the bare fiber in the pancreas head through trans-gastric or trans-duodenal approach. The ultrasonic imaging allows to visualize lesions up to 1-2 mm, and to target them avoiding the intervening vessels.

Di Matteo *et al.* [5] realized LITT-EUS guided procedure on pancreas of 8 healthy pigs, showing no post-procedure complications within 24 hours after therapy. They evaluated ablated volumes induced by laser therapy.

The novelty of present work is to implement the theoretical model of laser-tissue interaction in order to apply LITT to *ex vivo* healthy tissue and *in vivo* healthy and neoplastic one, and to establish the correlation between energy delivered per unit time and ablation volume.

In this study a Nd:YAG laser has been used, wavelength of 1064 nm in continuous mode (CW), guided by a thin and flexible optical fiber with 300 μm core diameter. We simulated the theoretical thermal response of healthy and neoplastic *in vivo* pancreatic tissue and healthy *ex vivo* tissue at different laser settings, showing a correlation between laser power and induced ablated volume. We compare *ex vivo* theoretical results with experimental data.

II. Mathematical Model

Human tissue warming was mathematically described by Pennes [6]. The so called *bio-heat equation* considered in the present work assumes the form:

$$\rho c \frac{\partial T(x,y,x,t)}{\partial t} = \nabla \cdot (k \nabla T(x,y,z,t)) + Q_b + Q_m + Q_{laser} \quad Q_e \qquad (1)$$

where ρ is the tissue density [kg m^{-3}], c is the specific heat [J kg^{-1} K^{-1}] and k is the heat conductivity [W m^{-1} K^{-1}]. $T(x,y,z,t)$ [K] is the tissue temperature, as a function of spatial coordinates x, y, z and time t [s]. Other terms in (1) are:

- Q_b, the heat generation due to blood perfusion per unit of volume:

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$$Q_b = \rho_b c_b w_b (T(x,y,z) - T_b) \quad (2)$$

being ρ_b the blood density [kg m^{-3}], c_b the blood specific heat [J kg^{-1} K^{-1}], w_b the blood perfusion rate per unit of volume [s^{-1}] and T_b the body temperature [K];

- Q_m the metabolic heat generation per unit volume, due to the oxidative process of lipids, carbohydrates and proteins;
- Q_{laser} the heat source term per unit of volume due to photon absorption caused by laser-tissue interaction:

$$Q_{laser} = a \cdot I(x,y) \cdot e^{-\alpha z} \quad (3)$$

being $I(x,y)$ [W m^{-2}] the laser irradiance, modeled using a 2D Gaussian distribution with σ equal to 50 μm in order to obtain the 99 % of the output laser power contained in the fiber surface (radius 150 μm):

$$I(x,y) = I_0 \cdot e^{-\frac{x^2+y^2}{2\sigma^2}} \quad (4)$$

where $I_0 = \frac{P}{2\pi\sigma^2}$, and P [W] is the output laser power, in continuous mode.

The laser-tissue interaction is described by Lambert-Beer law, which presents the absorption of electromagnetic monochromatic radiation in an irradiated medium in z-direction: α is the absorption coefficient [m^{-1}], that depends on the wavelength of laser radiation and on the tissue properties.

- Q_e represents the power density for water evaporation [7]:

$$Q_e = -\lambda \cdot \frac{d\rho_w}{dt} \quad (5)$$

where λ is the water's latent heat [J kg $^{-1}$] and ρ_w is water density [kg m^{-3}]; ρ_w is assumed to be only temperature dependent, according to equation (6). The introduction of Q_e in the model allows to consider the changing of tissue properties at high temperature. At 373.15 K water boils and induces cellular lysis, causing necrosis and the loss of physiological activity of cells. Equation (6) is applied under hypothesis that the whole water steam does not leave the system (closed system), that steam fills the tissue region at lower temperature and condenses uniformly [7]:

$$\rho_w(T) = \begin{cases} 0.778(1 - e^{\frac{T-379.15}{3.42}}) & T \le 376.15\ K \\ 0.0289T^3 - 8.924T^2 + 919.6T - 31573 & 376.15 < T < 377.15\ K \\ 0.778e^{-\frac{T-353.15}{3.42}} & T \ge 377.15\ K \end{cases} \quad (6);$$

- *Absorption and effective attenuation coefficient*

The proposed model considers the scattering phenomenon occurring in turbid media, e.g., biological tissues. By considering the "Photon Transport Theory" and, in particular, the "Diffusion Approximation" by Ishimaru [8], scattering and absorption phenomena are modeled by the effective attenuation coefficient α_{eff}:

$$\alpha_{eff} = \sqrt{3\alpha(\alpha + \alpha_s(1 - g))} \quad (7)$$

where α_s is the tissue scattering coefficient and g is the anisotropic coefficient. Thus, in present study, eq. (3) is modified replacing α with α_{eff}.

III. MODEL SIMULATIONS AND EXPERIMENTS

Scientific literature does not provide values of all mechanical, thermal and optical properties of pancreatic tissue needed in present model therefore, in some cases, we utilized liver properties values, since most pancreas properties as quite similar to corresponding liver properties.

TABLE 1
Physical and optical properties used in theoretical model

Symbol	Quantity	Value	Tissue	Reference
k	Heat conductivity [W m^{-1} K^{-1}]	0.5417	pancreas	[9]
ρ	Density [kg m^{-3}]	1040	pancreas	[10]
c	Specific heat [J kg^{-1} K^{-1}]	3590	liver	[3]
w_b	Blood perfusion [s^{-1}]	healthy 0.0253 neoplastic 0.0352	pancreas	[15]
α	Absorption coefficient [m^{-1}]	24	liver	[3]
α_s	Scattering coefficient [m^{-1}]	3x10^4	liver	[3]
g	Anisotropy coefficient	0.95	liver	[3]
λ	Latent heat [kJ kg^{-1}]	2260	water	[7]
ρ_b	Blood density [kg m^{-3}]	1060	blood	[11]
c_b	Blood specific heat [J kg^{-1} K^{-1}]	3640	blood	[11]

The model was implemented assuming values listed in table 1 for pancreatic tissue, blood and water properties. Tissue is considered homogeneous and isotropic. The effective attenuation coefficient α_{eff} is assumed equal to 331 m^{-1}, taking into account liver properties for α, α_s and g in table 1. Q_m is 33800 W m^{-3} [12]. The laser applicator is a single cylindrical bare fibre with 300 μm core diameter. The laser is Nd:YAG with wavelength of 1064 nm. The model was implemented in COMSOL 3.5a using a 3D geometry. As boundary conditions, infinite temperature is assumed equal to 310.15 K (body temperature).

A. Ex-vivo tissue analysis

Treatments were performed on *ex vivo* animal (pigs) pancreatic tissue utilizing laser energy equal to 1000 J for power values ranging from 1.5 W to 20 W (CW) and covering the clinical settings 3 W, 6 W and 10 W. Figure 1 shows the simulation result of temperature distribution in *ex-vivo* pancreatic tissue after treatment at 1.5 W lasting 666 s.

In this case, equation (1) assumes Q_b=0 (since w_b=0) and Q_m=0. In order to evaluate the tissue damage induced by laser irradiation we suppose that the region where T≥373.15 K can be associated with ablated region caused by hyperthermia, shown in fig. 1.b. The estimation of vaporized tissue volume in each treatment has been obtained supposing an ellipsoidal volume [13]

$$V_c = \frac{\pi}{6} dbh \tag{8}$$

where d, b and h are the axes length of the ellipsoid (fig. 1.a). *Ex vivo* measurements were realized in 30 porcine healthy pancreas undergone Nd:YAG-ultrasound (US) guided laser ablation using power values of 3 W, 6 W and 10 W, and delivered energy equal to 1000 J (CW). The V_c [mm^3] induced by Nd:YAG laser ablation was measured on histological specimens considering the surfaces showing absence of tissue (ablated region), and summing the ablated surfaces, measured on each slice, multiplied by the thickness of the slice. Test results are: P=3 W, V_c=40±30 mm^3; P=6 W, V_c=80±30 mm^3; P=10 W, V_c=100±20 mm^3.

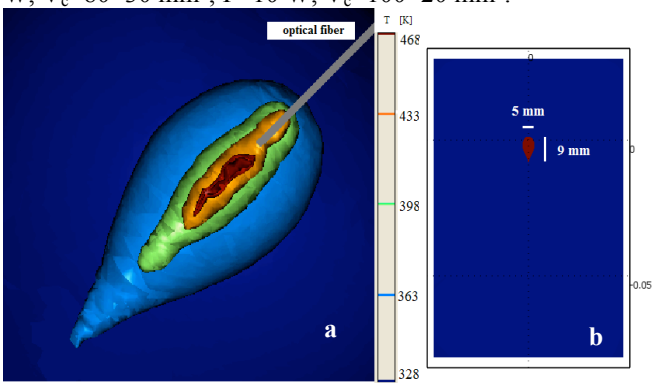

Fig. 1. Temperature distribution in *ex-vivo* pancreatic tissue after treatment at 1.5 W lasting 666 s. a- Placement of optical fiber in the tissue and isothermal surfaces after treatment; b- Region section (and relative quotes, h=9 mm, b=d=5 mm) in which temperature reaches 373.15 K.

B. In vivo tissue analysis

The model was implemented for evaluation of LITT applied to *in vivo* pancreatic tissue, considering the difference between healthy and neoplastic tissue: the pathologic case is realized with difference in blood perfusion, caused by tumor angiogenesis. In this case, blood perfusion w_b for healthy pancreatic tissue is 0.0253 s^{-1}, and for neoplastic one is 0.0352 s^{-1} [14]. The treatments were performed considering energy of 1000 J and power values ranging from 1.5 W to 20 W (CW).

IV. RESULTS AND DISCUSSION

The model evaluates *ex vivo* and *in vivo* treatments. We calculate the ablated volume obtained by laser application (8), which increases when output power increases from 1.5 W to 20 W. As far as it concerns *ex vivo* treatments, theoretical results are compared with experimental data: 30 porcine healthy pancreas underwent Nd:YAG-EUS guided laser ablation for power setting 3 W, 6 W and 10 W at 1000 J. Figure 2 shows the numerical prediction of healthy and neoplastic *in vivo* tissue, and the agreement between theoretical curve of numerical prediction (continuous curve, obtained fitting theoretical volumes) and clinical *ex vivo* measurements (black points). Experimental data, obtained through 10 measurements each power setting, are presented as mean ± expanded uncertainty. The expanded uncertainty is estimated by multiplying the standard deviation of the 10 measurements with a coverage factor of 2.26 obtained considering a Student's distribution with 9 degrees of freedom and a level of confidence of 95 % [15].

Experimental ablated volume values are quite in agreement with theoretical prediction, showing an increase of 61% if power increases from 3 W to 6 W, versus 46% obtained with experimental tests, and a theoretical increase of 14% from 6 W to 10 W, versus 21% shown by measurements.

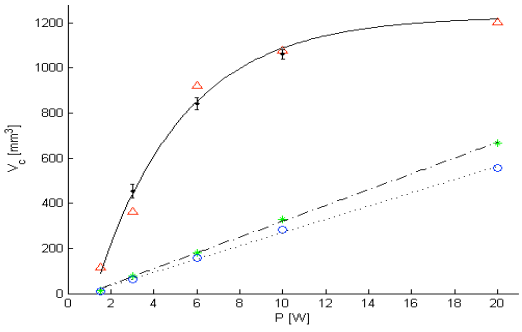

Fig. 2. Comparison between theoretical curve (continuous line), obtained by fitting theoretical *ex vivo* volumes (red triangles), and experimental (dots) ones V_c [mm^3] as a function of laser power [W]; ablated theoretical volumes of healthy *in vivo* pancreas (green asterisks) with linear best fitting curve (dash-dotted line) and ablated theoretical volumes of neoplastic *in vivo* pancreas (blue circles) with linear best fitting curve (dotted line), as function of laser power.

The best fitting curve found for ablated *ex vivo* tissue volumes is described by following equation

$$V_c = \beta(1 - e^{\gamma P}) + \delta \tag{9}$$

where β=1650 mm^3, γ=-0.2453 W^{-1}, δ=-420.3 mm^3 (R^2=0.97).

Figure 2 also shows different trend between V_c of *in vivo* healthy pancreatic tissue and V_c of *in vivo* neoplastic tissue, as a function of laser power: for the same energy and power settings, neoplastic ablated volume is smaller than healthy one, because of greater perfusion (tumour angiogenesis). The *in vivo* linear fitting curves are described by the equation:

$$V_c = \eta_i P + \varsigma_i \tag{10}$$

where, for i=healthy, η=35.04 mm^3 W^{-1} and ς=-30.56 mm^3; for i=neoplastic, η=29.39 mm^3 W^{-1} and ς=-24.19 mm^3. Pancreatic cancers with volumes bigger than simulated ones can be ablated through some back-to-back applications.

Laser-tissue interaction also shows a dynamic phenomenon in warming and cooling of treated tissue. Simulations allow the evaluation of tissue response time to irradiation (fig. 3), during the laser treatment, and after

stopping the therapy. Figure 3.a shows the dynamic of temperature in correspondence of tissue volume where maximum temperature T_{max} increases up to 644 K at the end of treatment (fig. 1.b): T reaches, in about 10 s, the 90 % of T_{max}, and keeps mostly constant, increasing very slowly, during the therapy. Interrupting laser irradiation, in the volume at T_{max} after 666 s, T decreases below 373.15 K in around 14 s (fig. 3.b, dash dotted line), while in surrounding regions T decreases more slowly during cooling.

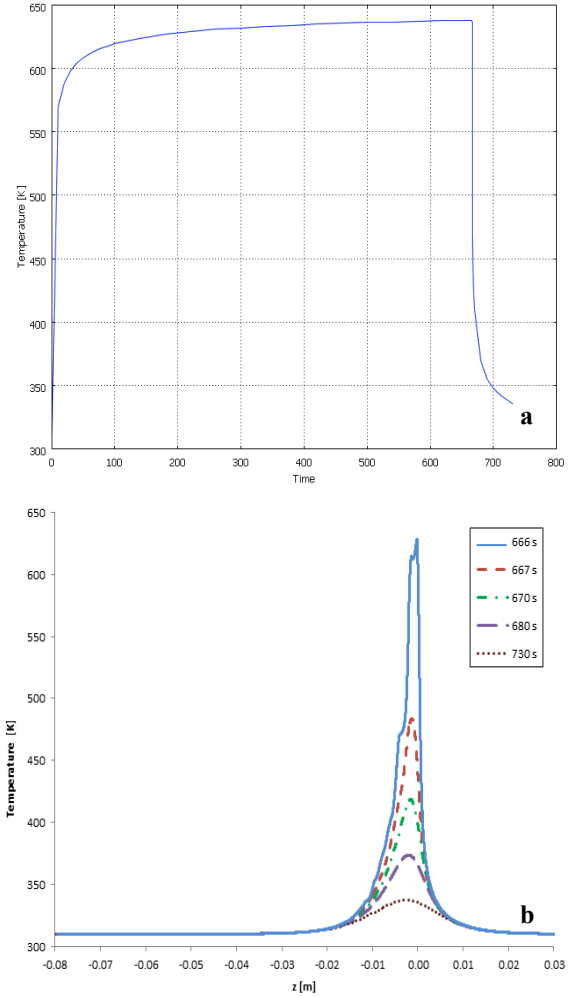

Fig. 3. Temperature as function of time (1.5 W). a- Dynamic of temperature [K] during laser therapy and cooling in correspondence of a small tissue volume where T reaches maximum value. b- Evaluation of temperature reached in pancreas at the end of laser therapy (666 s) and during cooling in z direction.

Above the estimation of ablated volume in *ex vivo* and *in vivo* pancreatic tissue, physical model is therefore also useful for temperature evaluation and for analyzing the dynamic of thermal phenomenon in warming and cooling; in fact, clinical practice and US images give no information about temperature reached in tissue during the treatment.

V. CONCLUSIONS

A theoretical model of laser-tissue interaction in order to estimate the dimensions of biological damage induced by LITT has been developed.

Simulations show an increase of ablated volume with laser power. The ablated volume of *ex vivo* healthy tissue (no perfusion) is greater than *in vivo* one. A further decrease is predicted in neoplastic *in vivo* tissue caused by tumor angiogenesis.

LITT has been performed on 30 porcine *ex vivo* pancreases; experimental results show a reasonable agreement of ablation volume as a function of laser power with theoretical ones.

Although the theoretical model should be refined, it may be useful to define correct laser settings in LITT of pancreas cancer; hopefully, it could be used as real time feedback tool for physicians willing to visualize the extension of removed tissue during LITT-EUS guided procedure.

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