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Theoretical assessment of principal factors influencing laser interstitial thermotherapy outcomes on pancreas

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***Abstract*— The influence of some therapy-relevant parameters on Laser Induced Interstitial Thermotherapy (LITT) outcomes on pancreas is assessed. The aim is to execute a sensitivity analysis for an optimal treatment strategy on *in vivo* pancreas. A numerical model based on Bioheat Equation has been implemented to assess the influence of laser settings (power P and energy E), applicator radius (r_f) and optical properties (effective attenuation coefficient, μ_{eff}) on temperature (T) distribution. Effects on pancreas undergoing LITT have been evaluated with a twofold approach: 1) T rise and maximum T (T_{max}) in tissue; 2) injured volumes (vaporized and coagulated ones). We consider parameters range in typical LITT values (P from 1.5 W to 6 W, E from 500 J to 1500 J, r_f from 150 µm to 600 µm) and optical values reported in literature. Our analysis shows that, among others, P and μ_{eff} are the principal influencing factors of thermal effects on pancreas undergoing LITT: P should be carefully chosen by operator to obtain the desired injured volumes, while the accurate measurement of tissue optical properties is crucial to carry out a safe and controlled thermal therapy on pancreas.**

I. Introduction

Laser is widely used in medical applications, mostly because of thermal effects. LITT is a particular application: it destroys neoplastic tissue through thermal coagulation and necrosis, induced by laser-tissue interaction. Continuous-wave laser energy is carried inside the deep seated neoplasia through a light guide, e.g., a quartz optical fiber. LITT is currently employed for ablation of neoplastic tissue in liver, prostate, lungs, and brain [1, 2]. A preliminary study regarding LITT application on pancreatic tissue has been conducted by Di Matteo *et al.* [3] on *in vivo* animal models. Since pancreas cancer management is still challenging for medical community, because of its high mortality and poor diagnosis, a big research effort has been made to assess the feasibility of LITT for pancreatic neoplasia treatment.

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Therapy-relevant parameters for a LITT procedure are laser power, P [W], and energy, E [J], duration of treatment, and fiber applicator radius, r_f [µm]. These parameters are chosen with the aim to injure the whole neoplastic region, avoiding the damage of healthy tissue. When tissue undergoes LITT, its injured volume depends on tissue temperature distribution, which plays a crucial role in the efficacy of treatment [4, 5].

In a previous study [6], a comparison between theoretical prediction and experimental data of LITT effects on *ex vivo* pancreas was performed. Although the study investigated the effects at different P values, a wider analysis considering different E and P and applicator size can be useful. Tissue temperature distribution is also related to tissue optical properties. Therefore, the absence of these values in scientific literature is an important issue for the theoretical prediction of LITT effects on pancreas [6].

This theoretical study investigates the thermal effects of LITT on *in vivo* pancreas considering some relevant parameters: both P and E are changed in a range commonly utilized in LITT; the influence of applicator size is also analyzed; this study purposes also to investigate the effects of optical properties on pancreas thermal distribution, in order to quantitatively evaluate tissue injury.

II. Theoretical Model

A. Tissue Optical Properties

Tissue optical properties govern propagation of laser energy in biological tissue and its transformation into thermal energy. This phenomenon, due to photons absorption and scattering, mainly depends on the anisotropic tissue structure. Optical properties, involved in description of laser-tissue interaction, are: absorption coefficient μ_a [m^{-1}], scattering coefficient μ_s [m^{-1}] and anisotropy coefficient g. They depend on wavelength of laser, and on tissue properties, as water, lipid and chromophore content. Optical albedo, a, is expressed as:

$$a = \frac{\mu_s}{\mu_s + \mu_a} \tag{1}$$

If a value is close to unity, biological tissue are classified as turbid media [7]. This happens in the typical LITT therapeutic window, ranging from 600 nm to 1200 nm, where scattering phenomenon is dominant respect to linear absorption. Accordingly to the Diffusion Approximation by Ishimaru, scattering and absorption phenomena are modeled by the effective attenuation coefficient μ_{eff} [m^{-1}]:

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s(1-g))} \quad (2)$$

μ_{eff} determines the amount of laser light penetrating into the tissue, and, therefore, the amount of laser energy converted into heat.

B. Laser Power Absorption

Laser beam is guided by an optical fiber (i.e., bare tip fiber) normal to the target surface. Its irradiance, I(x,y) [W·m^{-2}], is modeled using a 2D Gaussian distribution with standard deviation σ equal to $r_f/3$ (where r_f is the radius of optical fiber core) in order to obtain the 99% of power contained within the fiber core [8]:

$$I(x,y) = I_0 \cdot e^{-\frac{x^2+y^2}{2\sigma^2}} \quad (3)$$

$I_0 = \frac{P}{2 \cdot \pi \cdot \sigma^2}$ is the collimated irradiance [W·m^{-2}]. The laser heat source term Q_l [W·m^{-3}] is related to tissue optical properties according to the Lambert-Beer's Law, and can be expressed as:

$$Q_l = \mu_{eff} \cdot I(x,y) \cdot e^{-\mu_{eff} \cdot z} \quad (4)$$

C. Thermal Model (Bioheat Equation)

Power deposition in tissue causes temperature increase, that can be estimated by the Bioheat Equation [9]:

$$\rho \cdot c \frac{\partial T(x,y,z,t)}{\partial t} = \nabla(k \nabla T(x,y,z,t)) + Q_b + Q_m + Q_l - Q_e \quad (5)$$

where ρ is the tissue density [kg·m^{-3}], c is the tissue specific heat [J·kg^{-1}·K^{-1}] and k is the tissue heat conductivity [W·m^{-1}·K^{-1}]. $T(x,y,z,t)$ is the tissue temperature, expressed as function of spatial coordinates x, y, z and of time, t [s]. Tissue is assumed to be homogeneous and isotropic to make the heat transfer analysis more feasible and to maintain generality. Other terms in (5) are:

- Q_b [W·m^{-3}], the heat absorption due to blood perfusion per volume unit in the tissue:

$$Q_b = \rho_b \cdot c_b \cdot w_b(T(x,y,z,t) - T_b) \quad (6)$$

where ρ_b is the blood density [kg·m^{-3}], c_b the blood specific heat [J·kg^{-1}·K^{-1}], w_b the blood perfusion rate per volume unit [s^{-1}] and T_b the blood temperature outside the treatment site;

- Q_m [W·m^{-3}], the metabolic heat generation per unit of volume, due to oxidative process of lipids, proteins and carbohydrates;

- Q_e [W·m^{-3}] is the power absorption due to water evaporation [10]:

$$Q_e = -\lambda \cdot \frac{d\rho_w}{dt} \quad (7)$$

where λ is the water's latent heat [J·kg^{-1}] and ρ_w is the water density [kg·m^{-3}], that depends on T:

$$\rho_w(T) = \begin{cases} 0.778 \cdot \left(1 - e^{\frac{T-106}{3.42}}\right) & T \le 103\,°C \\ 0.0289 \cdot T^3 - 8.924 \cdot T^2 + 919.6 \cdot T - 31573 & 103\,°C < T < 104\,°C \\ 0.778 \cdot e^{\left(-\frac{T-80}{34.37}\right)} & T \ge 104\,°C \end{cases} \quad (8)$$

At 100 °C water boils and induces lysis, causing necrosis and the loss of physiological activity of cells. Equation (7) is applied under hypothesis that the whole water steam does not leave the system, that steam fills the tissue region at lower temperature and condenses uniformly.

Constant values are: for pancreas, ρ=1040 kg·m^{-3}, c=3590 J·kg^{-1}·K^{-1}, k=0.5417 W·m^{-1}·K^{-1}; for blood, ρ_b=1060 kg·m^{-3}, c_b=3640 J·kg^{-1}·K^{-1}, λ=2260000 J·kg^{-1}. Furthermore, the fluctuations of w_b and Q_m are considered negligible because they cause T variations lower than 1 K [11]. Therefore, also w_b and Q_m values are considered constant (w_b=0.0253 s^{-1} and Q_m=33800 W·m^{-3}). For the quartz fiber: ρ=2600 kg·m^{-3}, c=820 J·kg^{-1}·K^{-1}, k=3 W·m^{-1}·K^{-1}. For some constants, e.g., c and optical properties, pancreas values have been replaced with liver ones [2, 12], due to their absence in literature.

Theoretical study has been implemented in COMSOL Multiphysics 3.5a, considering a 3D geometry in order to model the pancreas and the applicator (quartz bare tip fiber). Initial tissue temperature and boundary conditions are T_0=T_∞=310.15 K.

III. Injured Tissue Volumes Prediction

Thermal injury in a living tissue undergoing LITT depends on T reached during treatment. T rise in pancreas entails observable effects within the tissue: in a preliminary *in vivo* study on porcine model, Di Matteo *et al.* [3] showed the presence, in treated specimens, of vaporized regions surrounded by coagulated ones, as shown in Fig. 1.B.

Fig. 1.A schematically shows theoretical assessment of injured volume size, as discussed by McKenzie [13], who considered two T thresholds without taking into account heating duration: for T>100 °C the cells water vaporization entails explosive expansion causing tissue removal. The tissue volume subjected to this phenomenon has been indicated with V_v; for T>60 °C, protein denaturation occurs: volume where this condition is met is indicated as V_c. V_v and V_c are calculated for each simulation setting.

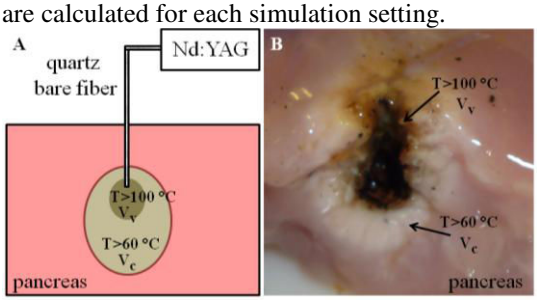

Figure 1. A) Schematic rapresentation of LITT procedure in pancreas and temperature thresholds; B) LITT effects on *in vivo* treated pancreas. V_c and V_v are the coagulated and vaporized volumes, respectively.

IV. Numerical Simulations: Results and Discussion

The aim of a numerical model is to provide a prediction of LITT effects considering several laser settings, tissue parameters and applicator types. Theoretical results should be useful to clinical operator in choosing optimal laser settings (P and E) and bare fiber radius (r_f). Furthermore, influence of tissue optical properties (μ_a, μ_s, g) has been assessed.

Thermal response of laser irradiated pancreas has been analyzed with a twofold approach: 1) evaluation of T rise in a point close to the laser applicator tip (e.g., distance of 3 mm) during treatment; 2) calculation of V_c and V_v using the abovementioned approach [13].

Simulations have been performed at different P, E, r_f, and μ_{eff}, as reported in Table I; in following subsections the influence of each parameter on LITT effects is described in detail.

TABLE I. Laser Settings, Applicator Radius and Effective Attenuation Coefficient Values Employed in Simulations.

P [W]	E [J]	r_f [μm]	μ_{eff} [m^{-1}]
1.5	500	150	311
3	1000	300	331
6	1500	600	623

A. LITT effects: P influence

Theoretical simulations have been conducted at different P values (Table I), and the effects on LITT outcomes have been evaluated in terms of T, V_c, and V_v as shown in Fig. 2.

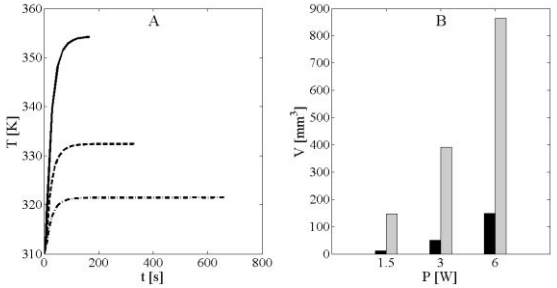

Figure 2. A) T rise, at 3 mm from fiber tip, vs t in pancreas undergoing LITT at 1.5 W (dash-dotted line), 3 W (dashed line) and 6 W (continuous line); B) V_v (black bar) and V_c (grey bar) at P from 1.5 W to 6 W.

Numerical results show that the higher P, the higher T rise in pancreatic tissue close to applicator (3 mm). For example, when E=1000 J, T reaches about 355 K at P=6 W, vs 321 K at 1.5 W (Fig 2.A). Similar results are obtained for V_c and V_v (Fig 2.B). In fact, the higher P, the higher V_v and V_c: increasing P from 1.5 W to 3 W, both V_v and V_c increase of about 2.8 times; from 3 W to 6 W, V_v triples (50 mm^3 vs 150 mm^3); on the other hand, V_c increases slightly more than double (391 mm^3 vs 867 mm^3). This trend quite agrees with *in vivo* trials on healthy pigs reported in a previous study by Di Matteo *et al.* [3]: at both E values (500 J and 1000 J), and r_f=150 μm, they found a V_c increase with P. When E=1000 J, they report V_c=483 mm^3 at 3 W vs V_c=460 mm^3 at 2 W. Definitively, P strongly influences T distribution and injured volumes on pancreas undergoing LITT, and therefore should be carefully chosen by clinicians.

B. LITT effects: E influence

Numerical simulations have been performed at different E values (table I), and effects have been assessed (Fig. 3).

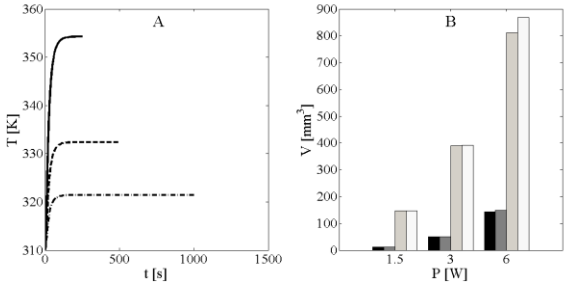

Figure 3. A) T rise, at 3 mm from fiber tip, vs t in pancreas during LITT at 1.5 W (dash-dotted line), 3 W (dashed line) and 6 W (continuous line) when E=1500 J; B) V_v at 500 J (black bar) and 1500 J (dark grey bar), and V_c at 500 J (grey bar) and 1500 J (white bar), at P from 1.5 W to 6 W.

Fig. 3.A shows that T_{max} is not influenced by E: T values at 1500 J (for three P values analyzed) are not subjected to variations respect to the treatment with 500 J (covered by black lines in the same picture), also V_v changes can be neglected. On the other hand, V_c is influenced by E: Fig. 3.B shows that at 6 W, V_c increases from 799 mm^3 at 500 J to 884 mm^3 at 1500 J.

C. LITT effects: r_f influence

Numerical simulations have been performed for different r_f values (table I), and effects have been evaluated (Fig. 4).

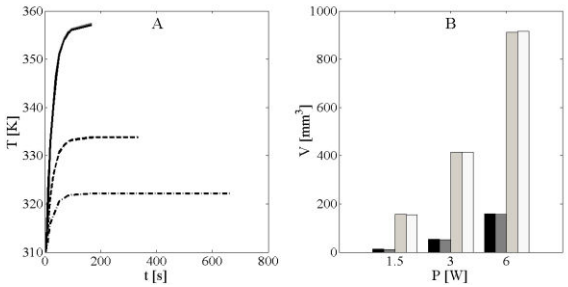

Figure 4. A) T rise, at 3 mm from fiber tip, vs t in pancreas undergoing LITT at 1.5 W (dash-dotted line), 3 W (dashed line) and 6 W (continuous line); B) V_v at 300 μm (black bar) and 600 μm (dark grey bar), and V_c at 300 μm (grey bar) and 600 μm (white bar), at P from 1.5 W to 6 W.

The effects of r_f variation are not significant on T rise, as observable in Fig. 4.A, where the T rise curve for r_f=300 μm and the same curve obtained at 600 μm are overlapped. In Fig. 4.B it is shown a slight influence of r_f on V_v and V_c, decreasing with P: for example, at 3 W, increasing r_f from 300 μm to 600 μm, V_v decreases from about 51 mm^3 to about 30 mm^3 (decrement of 40%), and V_c drops from 425 mm^3 to 391 mm^3 (decrement of about 8%); on the other hand, at 6 W, V_v decreases from 159 mm^3 to 131 mm^3 (decrement of 19%), and V_c changes from 918 mm^3 to 884 mm^3 (decrement of about 4%).

D. LITT effects: μ_{eff} influence

Optical information about pancreas lack, but literature reports data about optical properties of biological media, in particular of tissues commonly undergoing LITT for cancer

removal, i.e., liver and prostate. Although evaluated at wavelength relevant for LITT, optical properties are not known with great accuracy. For example, many authors provide several values for liver properties (μ_a, μ_s, g and, consequently, μ_{eff}), that difference strongly each another, as observable in Table II:

TABLE II. HUMAN LIVER OPTICAL PROPERTIES AT 1064 nm.

μ_a [m^{-1}]	μ_s [m^{-1}]	g	μ_{eff} [m^{-1}]	reference
70	35600	0.95	623	[2]
30	15000	0.93	311	[9]
24	30000	0.95	331	[6]

In our study, values in Table II have been substituted in (2) and (4). Simulations have been performed at μ_{eff} equal to 311 m^{-1} and 623 m^{-1} (Fig. 5).

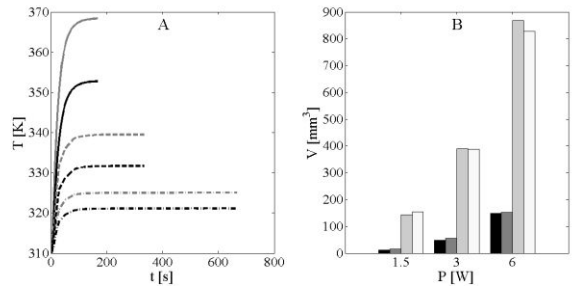

Figure 5. A) T rise, at 3 mm from fiber tip, vs t in pancreas undergoing LITT at 1.5 W (dash-dotted line), 3 W (dashed line) and 6 W (continuous line); B) V_v at 311 m^{-1} (black bar) and 623 m^{-1} (dark grey bar), and V_c at 311 m^{-1} (grey bar) and 623 m^{-1} (white bar), at P from 1.5 W to 6 W.

Numerical calculations show that T_{max} increases with μ_{eff} (Fig. 5.A): at 1.5 W, T_{max} raises from 320 K to 324 K (increment of about 1 %), at 3 W, from 330 K to 340 K (increment of 3 %), and at 6 W it increases from 351 K to 368 K, with an increment of 5 %. Therefore, the change in optical properties modifies the punctual T value reached at a fixed point from the quartz fiber tip (i.d., 3 mm), despite the influence on injured volumes. In fact, V_c and V_v are not subjected to a significant variation respect to T_{max}. Fig. 5.B presents the increment of V_v reducing with P when μ_{eff} is 623 m^{-1}: for example, at 1.5 W, V_v values 9 mm^3 if μ_{eff}=311 m^{-1} and it doubles at 18 mm^3 if μ_{eff}=623 m^{-1}; *vice versa*, at 6 W V_v is about 150 mm^3 for both μ_{eff} values. V_c shows the same trend: at 1.5 W, V_c at 311 m^{-1} is less than V_c at 623 m^{-1} (136 mm^3 vs 153 mm^3), but at 6 W this trend changes, resulting 867 mm^3 at 311 m^{-1} vs 833 mm^3 at 623 m^{-1}.

V. CONCLUSION

Theoretical assessment of therapy-relevant parameters for a LITT procedure on *in vivo* pancreas should be useful to choose the optimal laser settings, therefore the effects of P, E, r_f and μ_{eff} on pancreas thermal distribution have been analyzed. As expected, P is the most influencing parameter in T rise, T_{max}, V_v and V_c. On the other hand, μ_{eff} mainly influences T rise and T_{max}; variations are also appreciable in V_c and V_v values, particularly at 1.5 W and 6 W. Lastly, simulations show negligible effects of E and r_f. As far as it concerns E, the no appreciable effects on V_c and V_v could be due to the simple approach in their estimation [13]. Further investigations could be carried out to analyze effects of time-temperature history on pancreatic tissue.

In summary, P is the principal influencing parameter, as also experimentally demonstrated [3], it should be carefully defined to perform an optimal LITT procedure on *in vivo* pancreas by clinicians. Moreover, in order to avoid that numerical models fail in prediction of optimal settings, this study evidences the importance of an accurate estimation of tissue optical properties.

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