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A Method of Controlled Skin Surface Cooling During Photodynamic Therapy and Hyperthermia Treatment

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Abstract—A method and a fiber-optic device with an electronic cooling system were developed for controlled cooling of the skin surface during contact irradiation of intradermal tumors and metastases. Theoretical calculations and experiments on biological tissues with the use of the method developed gave closely agreeing results. These data indicate that local temperatures required for hyperthermia in deep layers of biological tissues can be achieved without injuring the surface layers. The fiber-optic device with the electronic cooling system is successfully applied in the clinic.

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INTRODUCTION

Hyperthermia and photodynamic therapy are methods of tumor and metastasis treatment based on the interaction of laser radiation with biological tissues [1]. Photodynamic therapy employs laser power densities of 400 mW/cm^2, on the average. For hyperthermia treatment procedures, infrared radiation is used. The absorption of laser radiation by biological tissue leads to a local increase in the tissue surface temperature, causing pain in patients.

The hyperthermia treatment is conducted at temperatures ranging from 42.5 to 44–45°C [2]. Clinical applications often require irradiating deep tissue layers without damaging surface layers. Skin temperatures above 43°C cause pain in patients and inflict irreversible damage to healthy tissues. Therefore, to preserve intact the surface layers and physiological condition of patients subjected to photodynamic therapy and hyperthermia treatment it is necessary to reduce the upper tissue temperature. In cosmetics, e.g., in hair and vascular defect removal, the skin surface is cooled by devices whose working area contacts the heated area via the cooled surface. The working body of the devices is a refrigerant circulating inside the device, which passes through the contact surface and cools it. Such devices have fairly large dimensions, which make their use inconvenient.

These exists an alternative cooling method based on pulse spray cooling with R-134a refrigerant [3]. Prolonged use of this agent may cause central nervous system effects, whereby its use in the clinic is significantly limited.

Here, we report the development of a method and device for controlled cooling during contact irradiation of intradermal tumors and metastases. The device is compact and convenient for repeated use.

Theoretical Model

The heat distribution in the process of irradiation of a biological tissue by a point light source is described by the one-dimensional heat-conduction equation for a semi-infinite homogeneous medium [4]:

$$\frac{\partial T}{\partial t} = \frac{\gamma}{\rho_t c_t} \frac{\partial^2 T}{\partial x^2} - \frac{\rho_b c_b}{c_t} m(T - T_b) + \frac{I_0}{\rho_t c_t L} \exp(-x/L), \quad (1)$$

where x is the coordinate; t, time; $T(x, t)$, temperature distribution function; T_b, blood temperature; γ, coefficient of thermal conductivity of the biological tissue; ρ_t and ρ_b, tissue and blood densities, respectively; c_t and c_b, specific heats of the tissue and blood, respectively; m, blood flow velocity per unit mass of the tissue; I_0, laser power density on the irradiated surface; and L, depth at which the laser radiation power decreases by the factor of e.

The last two terms on the right-hand side of the equation describe the heat flux variation. Among them, the first term takes into account the temperature change due to blood circulation, and the second term, the heat influx due to radiation absorption.

The boundary condition for the contact surface cooling process can be written a follows:

$$\left.\frac{\partial T}{\partial x}\right|_{x=0} = -\frac{k}{\gamma}\,[T_c - T(0, t)], \qquad (2)$$

where k is the heat transfer coefficient between the sapphire plate (working part of the cooled device, see below) and the upper tissue layer, and T_c, temperature of the cooling surface.

The stationary solution to this equation is represented by the equation:

$$T(x, \infty) = \frac{I_0}{\gamma L(b - L^{-2})}\left[\exp\left(-\frac{x}{L}\right) - \frac{\gamma/L + k}{\gamma\sqrt{b} + k}\exp\left(-\sqrt{bx}\right)\right] + (T_c + T_b)\frac{k}{\gamma\sqrt{b} + k}\exp\left(-\sqrt{bx}\right) + T_b,$$

$$b = \frac{\rho_b \rho_t c_t m}{\gamma}\cdot \qquad (3)$$

We used Eq. (3) for theoretical calculation of the temperature distribution inside laser-irradiated biological tissues. It should be noted, however, that this equation does not take into account the change in the blood flow during irradiation and the depth at which the laser radiation power decreases by the factor of e. The change in the blood flow velocity is due to body regulation during local heating, and that in the irradiation depth, to the changes in the optical properties of biological tissues, caused by heating.

EXPERIMENTAL

Theoretical calculations showed that temperatures of 43–46°C, sufficient for deep tissue hyperthermia, can be achieved without injuring surface layers of the tissue. Hence, the main task to be accomplished during hyperthermia treatment procedure consists in providing effective heat removal from the irradiated area.

With this objective in view, we developed a device with an electronic cooling system for contact irradiation of intradermal tumors and metastases. The functional configuration of the cooling system (Fig. 1) includes an actuator and an electronic unit. The actuator is a unitary structure whose housing accommodates a Peltier module, a temperature sensor, a heat sink, and an SMA-type connector for mounting the fiber-optic system delivering the laser light from the source. The laser radiation delivery system consists of quartz-polymer fibers with the diameter of 600 μm and aperture of 0.31. To avoid optical radiation losses, additional optical system was not used in the actuator. The radiation exits through an end-face of the optical fiber as a cone of light, whose flat divergence angle varies with the fiber aperture.

The biological tissues are heated under laser irradiation (wavelength 600–1100 nm). The contact surface of the device is made of sapphire. This is an optically transparent material having a high thermal conductivity (46.06 W m^{-1} K^{-1} at 26°C) and a high melting point (2050°C); it remains pure at high temperatures and is resistant to scratching and high pressures. The transmittance of sapphire in the 400–1000 nm region is ~85%. This material is easily washed clean and has a long lifetime.

The sapphire window is cooled by a Peltier element converting the electric current that flows through it into the temperature difference between the "hot" and "cold" sides of the module [5].

For maintaining the temperature within the preset range, a temperature feedback system is used. On the sapphire glass, a temperature sensor is mounted which transmits the signal to the input of the proportional-integral-differential (PID) controller and to the input of the display unit. The PID controller provides for stabilization of the temperature setpoint. The display unit indicates the skin surface temperature based on the signal coming from the temperature sensor. The operating temperature range is conditionally divided into three areas: <26°C, 26–40°C, and >40°C.

The hyperthermia treatment procedure is carried out with an LFT-02-BIOSPEK diode laser (radiation wavelength 810 nm, power up to 9 W).

In our experiment, liver and muscle tissue of pigs served as models. Table lists the biological tissue characteristics used for calculating the temperature distribution in the tissues when cooled by the method proposed [5–8].

RESULTS AND DISCUSSION

Our calculations show that temperatures required for hyperthermia treatment deep inside the biological

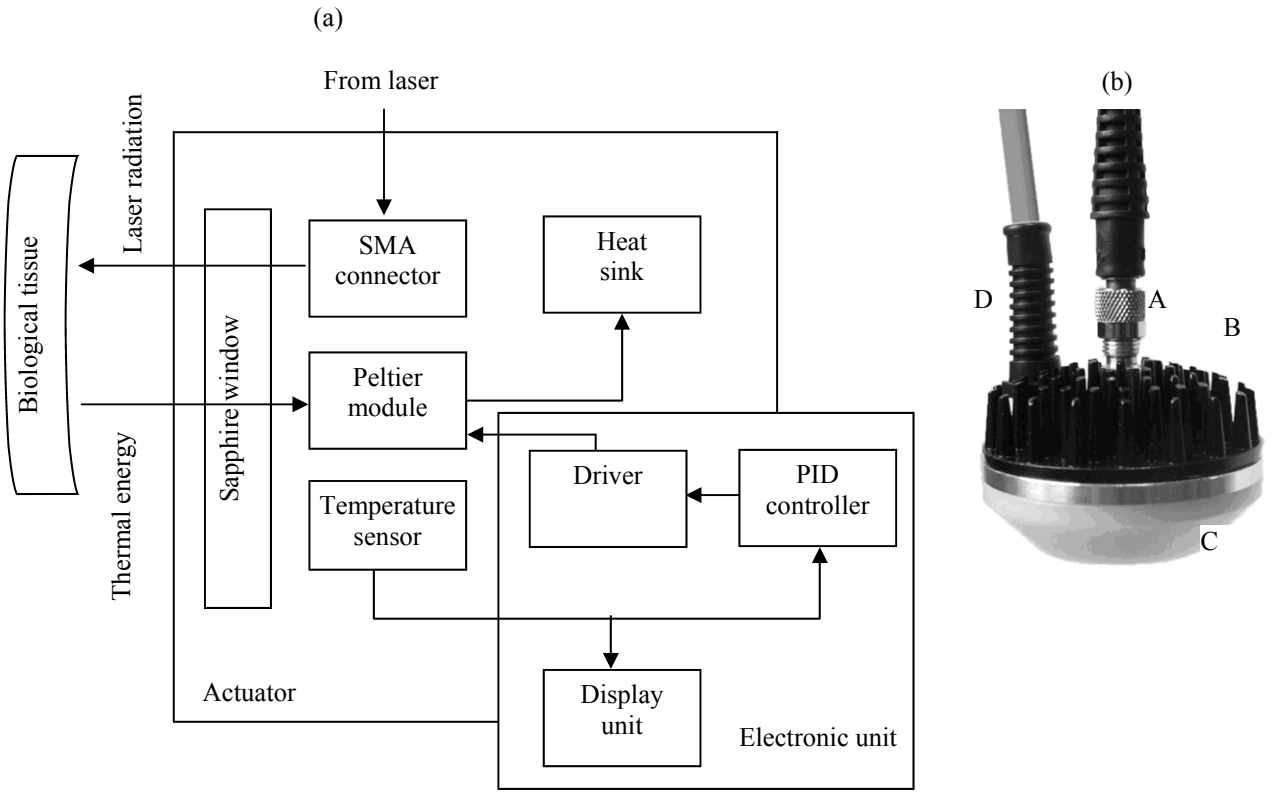

Fig. 1. Device with electronic cooling system for contact irradiation of intradermal tumors and metastases: (a) block diagram and (b) actuator: (A) SMA-905 connector for mounting the optical fiber, (B) round pin-fin heat sink, (C) casing made of a dielectric material with a sapphire window (at the bottom), and (D) electrical wire casing.

tissues can be achieved without damaging the surface layers of the tissues. Figure 2 presents the dependences of the tissue temperature on the laser radiation penetration depth as calculated by formula (3) for the two types of biological tissues, the skin and muscle tissue.

The hyperthermia temperature range shifts with depth at different laser power densities and sapphire window temperatures. The therapeutic effect can reach 4-mm depths, while the surface layer temperature below 40°C is preserved. With increasing laser power

Parameters for calculating the temperature distribution in biological tissue

Parameter	Value	
Blood temperature T_b, °C	37.35	
Blood density ρ_b, 10^{-3} kg/m^3	1.057	
Specific heat of blood c_b, kJ kg^{-1} K^{-1}	3.9	
Blood flow velocity m, cm/s	2	
Tissue type	Liver	Muscle tissue
Thermal conductivity of tissue γ, W m^{-1} K^{-1}	0.57	0.53
Tissue density ρ_t, 10^{-3} kg/m^3	1.05	1.01
Specific heat of tissue c_t, kJ kg^{-1} K^{-1}	3.6	3.7
Depth corresponding to radiation attenuation by the factor of e L, cm	0.058	0.094
Tissue/sapphire heat transfer coefficient k, W m$^{-2/}$K	2600	

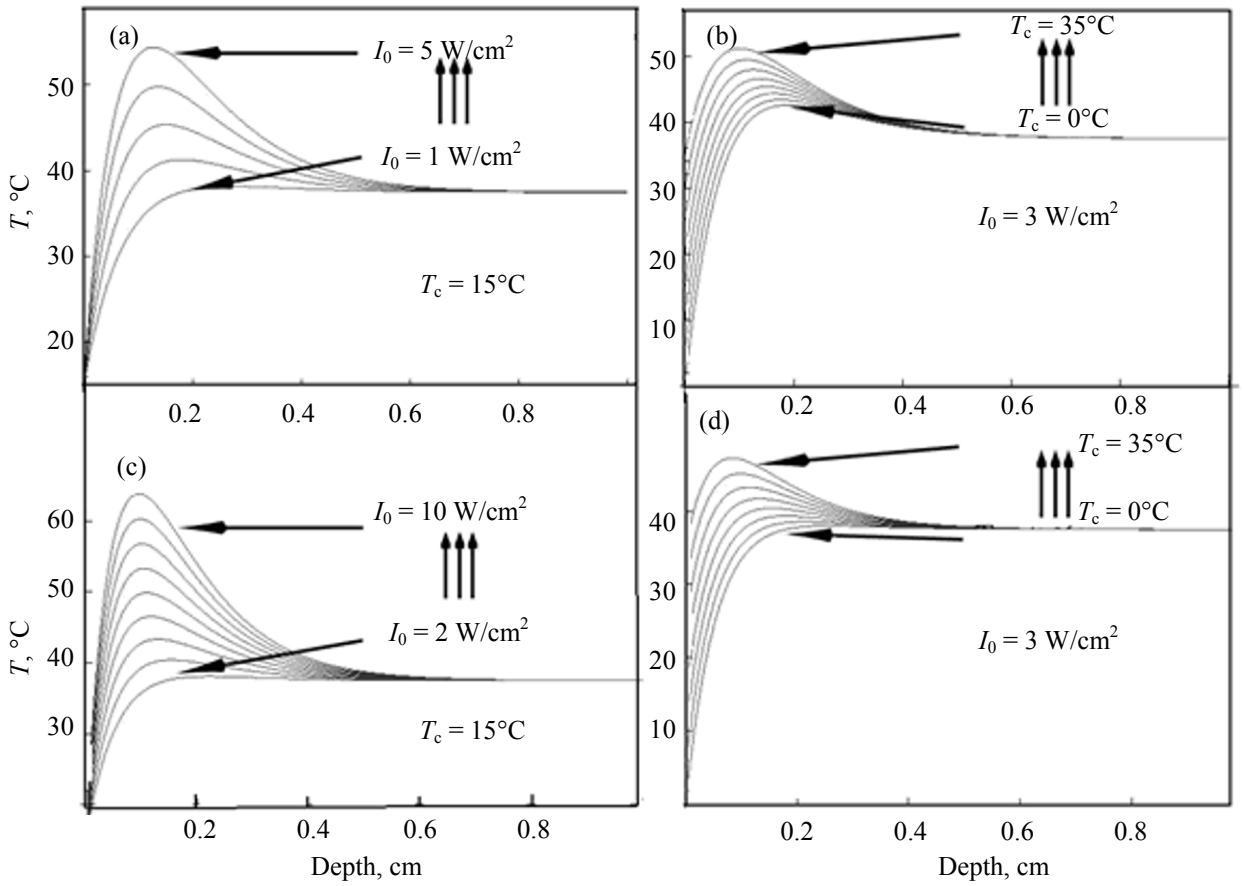

Fig. 2. Theoretical dependences of the biological tissue temperature on the laser radiation penetration depth: (I_0) laser power density and (T_c) sapphire window temperature. (a, b) Muscle tissue and (c, d) skin.

density (Figs. 2a and 2c) the temperature range approaches the surface layer temperature; with decreasing temperature of the cooling surface (Figs. 2b and 2d) it gets farther from the surface temperature of biological tissue.

Figure 3 shows a section of the liver tissue, obtained after 3-min irradiation with the use of the electronic cooling system. The upper boundary of the coagulation zone (bright spot in Fig. 3) is located at a distance of 0.5 mm, and the lower boundary, at a distance of 2.5 mm from the biological tissue surface. The width of the coagulation zone, which is dependent on the irradiated surface area, was 2.2 mm at the irradiated surface area of 1.8 cm^2 in our experiment. Shown in Fig. 3 is not only the coagulation zone but also the direction of the laser beam propagation in the biological tissue (with liver as an example).

We measured the temperature distribution in deep layers of the tissue whose surface was laser-irradiated (wavelength 810 nm) using the device with the electronic cooling system. The laser powers were 3 and 4 W, and the sapphire window temperature, 27°C.

Figure 4 presents the experimental data and the theoretical curves demonstrating the temperature distribution within the tissue at the laser radiation powers used. The temperature maximum is attained at a distance of 0.9 and 1 mm for laser powers of 4 and 3 W, respectively. The difference between the experimentally measured and theoretically obtained maximum temperatures lies within 5% for the respective laser radiation powers. During the radiation exposure, the tissue surface temperature remained constant, below 43°C. This means that patients subjected to hyperthermia treatment procedure using the fiber-optic device with the electronic cooling system will not feel pain, and the surface layers of the biological tissue being irradiated will not be damaged. By varying the irradiation parameters, in particular, the

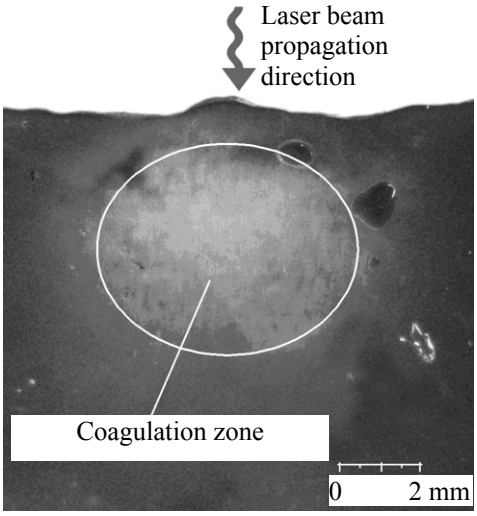

Fig. 3. Liver tissue section after 3-min irradiation (λ = 810 nm, power 3 W). (Bright spot) Coagulation zone formed during hyperthermia.

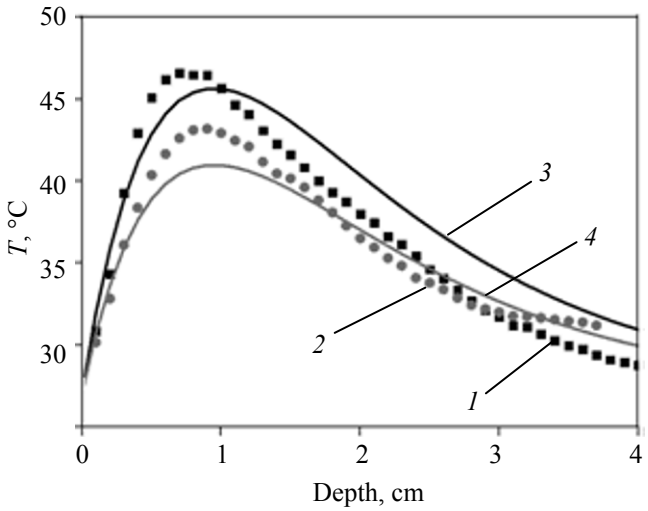

Fig. 4. Variation of the tissue temperature with the distance from the surface. Experiment: (*1*) 4 W and (*2*) 3 W and calculation: (*3*) 4 W and (*4*) 3 W.

sapphire window surface temperature and the laser power, it will be possible to treat tumors deep inside the body, thereby enhancing the effectiveness of hyperthermia treatment.

To conclude, the system developed by us has been usefully employed for treatment of metastatic breast cancer and primary skin and mucosa cancers in clinics of the city of Moscow. The device for local hyperthermia treatment is suitable for conducting photodynamic therapy sessions combined with hyperthermia to the full extent in highly sensitive areas.

CONCLUSIONS

Semi-empirical calculations show that, using the method of controlled skin surface cooling, local temperatures required for hyperthermia can be achieved in deep layers of biological tissues, while the physiological temperature range is preserved in the surface layers. Thereby, damage to healthy skin surface during photodynamic therapy and hyperthermia treatment will be avoided.

The results obtained for the biological tissues that were used in our experiments are in good agreement with the calculated data; deviations are due to the lack of blood flow in these tissues.

The fiber-optic device with the electronic cooling system, developed by us, is efficient in contact irradiation of intradermal tumors and metastases in the clinic.

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