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Event: Saratov Fall Meeting 2017, 2017, Saratov, Russian Federation

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ABSTRACT

We have developed cryoapplicators based on the sapphire shaped crystals fabricated using the edge-defined film-fed growth (EFG) and noncapillary shaping (NCS) techniques. Due to the unique physical properties of sapphire – i.e. high thermal, mechanical, and chemical strength, impressive thermal conductivity and optical transparency, these cryoapplicators yield combination of the tissue cryodestruction with its exposure to laser radiation for controlling the thermal regimes of cryosurgery, and with the optical diagnosis of tissue freezing. We have applied the proposed sapphire cryoapplicators for the destruction of tissues *in vitro*. The observed results highlight the prospectives of the sapphire cryoapplicators in cryosurgery.

Keywords: sapphire shaped crystals, cryosurgery, cryodestruction, laser thermotherapy

1. INTRODUCTION

Cryodestruction of biological tissues is based on their necrosis due to the freezing and thawing of tissue cells.[1] This process is effectively applied for surgical treatment,[2–7] since cryodestruction possesses significant advantages compared to the surgical resection[8,9] – i.e. lower invasiveness, low morbidity and bleeding, and short recovery period. Moreover, this technique demonstrates significant therapeutic effects, such as a stimulation of the tissue regeneration, an activation of the local immune response, a control of the analgesic and the anti-inflammatory processes.[10–12] An efficient cryodestruction requires the special instruments, which provide an increased capacity of the heat exchange, a control of the freezing volume, an opportunity of the tissue state diagnosis, a combination of various tissue effecting methods, and a control of the freezing depth and the destruction of tissue.[13,14]

Common instruments of the cryodestruction contain metal applicators – i.e. copper tips, which feature several evident drawbacks. First, the metal applicators are optically opaque and do not allow for delivering the laser radiation to the metal tip – tissue interface. Thus, the metal cryoapplicators can not be combined with the optical diagnosis of the tissue state. Second, the metal applicators posses rather thick porous oxide layer on the surfaces of the tip. This layer prevents effective sterilization due to the bacterial growth. Therefore, such tips should be covered by nickel or chrome coatings, which reduces the cryosurgery efficiency owing to the heat dissipation. Third, the ductility of copper prevents from steadiness of the tips' geometry, making them non-effective for the interstitial cryosurgery, where the sharp edges are required. Finally, while using the copper tips, one should account for the technical difficulties, associated with the heat fluxes through the copper components. Thus, the development of novel cryoapplicators, which overcome the listed drawbacks, is of high importance. For the intraoperative control of the ice ball formation, the cryodestruction should be combined with the modern

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Saratov Fall Meeting 2017: Optical Technologies in Biophysics and Medicine XIX, edited by Elina A. Genina, Irina Yu. Goryacheva. Valery V. Tuchin, Proc. of SPIE Vol. 10716, 1071615
 · doi: 10.1117/12.2306134

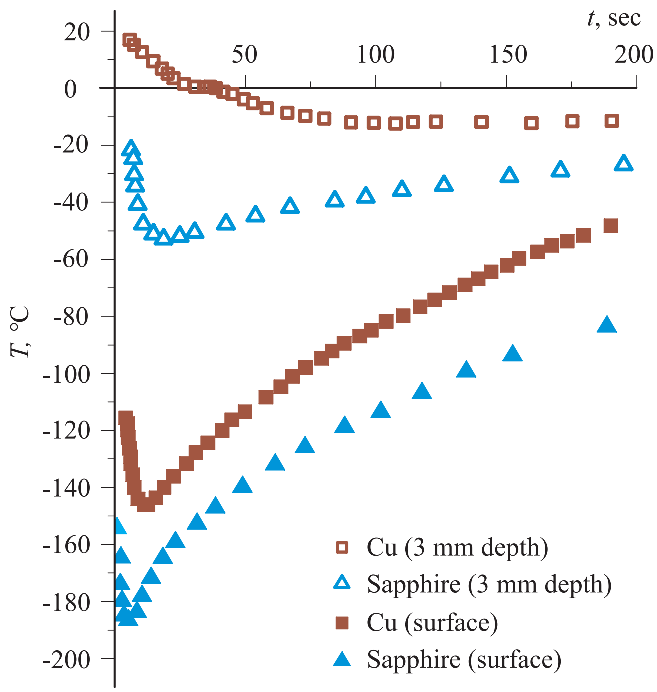

Figure 1. A comparison of the time-dependent temperature $T(t)$ provided by either the sapphire or metal cryoapplicators both at the cryotip – tissue contact and at the depth of 3 mm in tissue.[33]

methods of the real-time visualization of tissues, such as optical imaging relying on the effects of elastic or inelastic light scattering,[15–23] optical coherence tomography,[24–26] or terahertz imaging.[27–29]

In order to mitigate the listed drawbacks of the conventional metal tips, we suggest using the sapphire shaped crystals for production of the new type of cryoapplicators, which combine high hardness, chemical resistance, inertness to human body fluids, high thermal conductivity at the cryogenic temperatures, high refractive index, optical transparency in visual, infrared, and terahertz spectral ranges.[30] In comparison with the conventional copper tips, the sapphire cryoapplicators intensively dissipate the heat from the sapphire – tissue contact. Figure 1 shows that high thermal conductivity of sapphire significantly increases the rate of tissue cooling, which is of great importance for the deep freezing and the destruction of tissues (especially, of the malignant ones) within the selected area of cryosurgery. The unique thermal properties of sapphire is important for the tissue thawing, since the effects of thawing depend on the previous cooling rate.[6,31] A slow thawing leads to the solute effects and the maximum ice growth during the recrystallization. Because the solute effects and the ice growth are deleterious to cells, a complete thawing before the start of another cycle of freezing is essential and determines the success of cryosurgery.[32] The cooling rate is significant in case of cryosurgery of malignant tissues, since the normal and malignant tissues have different response to freezing due to different tissue hydration.[32] Sapphire cryoapplicators have a potential to provide an improved cryodestruction efficiency and an opportunity to control the ice ball formation during the process of the deep local freezing of tissues and allow for delivering the laser radiation to the cryoapplicator – tissue interface (for example, using the optical fibers) for diagnostics and exposure of tissues.[33,34]

2. MANUFACTURING THE SAPPHIRE CRYOAPPLICATORS

The sapphire cryoapplicators of various shape, including the monolithic and hollow ones, were grown directly from the Al_2O_3-melt by the edge-defined film-fed growth (EFG)[35] and the noncapillary shaping (NCS)[36] techniques, which are based on the Stepanov's concept.[37]

In the EFG technique, the sapphire shaped crystal is grown from a melt film formed on the top of a wettable die made of molybdenum, where the melt rises to the crystallization front through the capillary channel. This technique allows for producing the cost-effective sapphire crystals, which feature various cross-sections (rods, fibers, tubes, ribbons, etc.) and high-quality of as-grown surfaces, and could be used for a broad range of application.[38–41] Recently, the sapphire shaped crystals containing longitudinal capillary channels in their volume have been produced for application in biomedicine,[42–45] terahertz technology,[46,47] atomic emission spectroscopy,[48] etc. Figures 2 (a) and (b) show representative examples of the EFG-grown sapphire immersion-type cryoapplicators with the capillary channels in their volume. These cryoapplicators were grown in an automated way using the system of the crystal weight control, which provides *in situ* monitoring of the crystal quality.[41,49]

The NCS method allows for growing the sapphire shaped crystals featuring large cross-sections. This technique also employs a wettable die, but, in contrast to the EFG method, it does not require a capillary channel for lifting the melt from the crucible to the top of the die – i.e. the melt is delivered to the growth interface through a non-capillary channel. The NCS-grown sapphire shaped crystals possess high volumetric and surface quality with no microvoids, gaseous or solid inclusions. Sapphire monolithic crystals of any predetermined cross-section, which could be either constant or variable along the growth direction, can be produced by the NCS technique.[50,51] Figures 2 (c) to (e) show representative examples of the hollow filling-type sapphire cryoapplicators grown by the NCS technique.

Various geometries of the tip can be used to control the shape of the ice ball formed in tissues. As shown in Fig. 3, the tapered hollow cryoapplicator produces the ice ball featuring the oviform shape, while the flat tip yields the conventional hemispherical ice ball. Therefore, an appropriate geometry of the cryotip can be selected in order to localize the tissue freezing, which is essential for the long term cryodestruction.

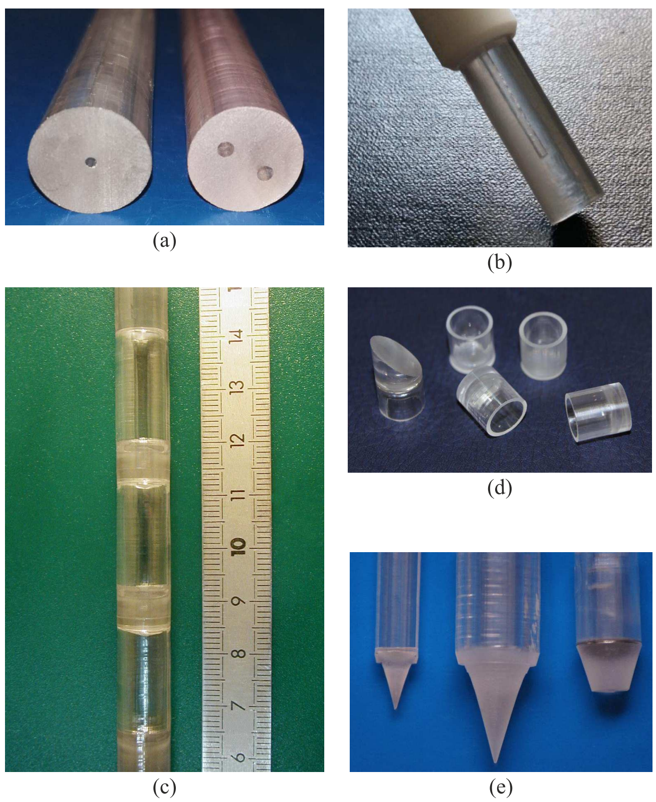

Figure 2. Cryoapplicators based on the sapphire shaped crystals: (a) an image of the EFG-grown sapphire rods containing the longitudinal capillary channels in their volume; (b) an image of the immersion-type cryoapplicator with the closed capillary channel; (c) an image of the NCS-grown sapphire shaped crystal featuring multiple transitions from the monolith to the hollow parts; (d) an image of the flat hollow filling-type sapphire cryoapplicators; (e) an image of the tapered hollow filling-type sapphire cryoapplicators.

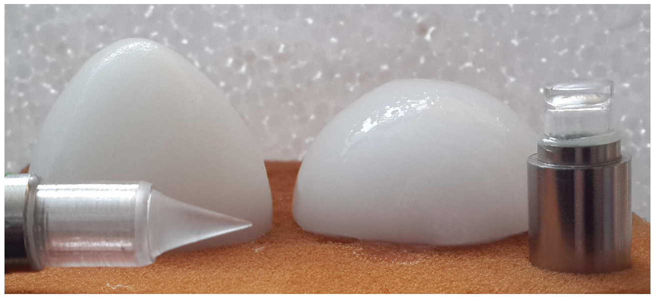

Figure 3. An image of the two types of the sapphire hollow cryoapplicators, which feature different geometry of the tip and, thus, different shape of the ice ball frozen in a model gel (a starch liquor).

3. DELIVERING THE LASER RADIATION TO TISSUES

Sapphire cryoapplicators allow for delivering the optical radiation to tissues for their diagnosis and laser thermotherapy during the cryosurgery. This can improve the efficiency of tissue targeting, which is of great importance for the tumor oncolysis. For this purpose, the sapphire cryoapplicators can be manufactured with the longitudinal channels in their volume. These channels are convenient for placement of the optical fibers, which can be attached to light sources and spectroscopic systems. Furthermore, the channels could be closed directly during the growth process with the sapphire membrane (or window) featuring either a plane-parallel shaped or a complex geometry. This helps protecting the optical fibers from interactions with tissues and allows for achieving the required distribution of the optical field in the tissue volume.

Figure 4 demonstrates an example of the immersion-type sapphire cryoapplicator, combining the cryodestruction with the laser control of the temperature regimes of the cryosurgery. In this cryotip, the laser radiation is delivered to the area of cryodestruction via a quartz optical fiber. Figures 5 (a) to (e) illustrate the cryodestruction of a liver tissue *in vitro* with the 2-min-duration cryoapplication followed by the 4-min-duration exposure of tissues to the 5 W/cm^2-average-power radiation of the 810 nm continuous-wave diode-pumped laser. Figures 5 (b) to (f) demonstrate the time-dependent temperature $T(t)$ at the cryotip – tissue interface. As shown in Fig. 5 (g), the increase of the tissue temperature from about -175°C to -55°C occurs due to the spontaneous heating. Then, the increase of the temperature to almost $+150$°C is driven by the 6-min-duration exposure of tissues to the laser radiation.

For a sapphire cryoapplicator with the contact area diameter of 10 mm, a typical volume of frozen and coagulated tissues is about 230 mm^3. For this typical ice ball and the irradiance of the sample surface up to 20 W/cm^2, we did not observe the contact sticking and the tissue gripping. By removing these negative effects of cryosurgery, which could lead to the traumatic removal of the instrument, we are able to significantly improve the cryodestruction efficiency. Finally, we should stress another important feature of the proposed favorable combination of tissue cryodestruction with its exposure to laser radiation – it allows for obtaining maximal tissue destruction by its freezing, and maintain hemostatic control in tissue by its laser heating.[32]

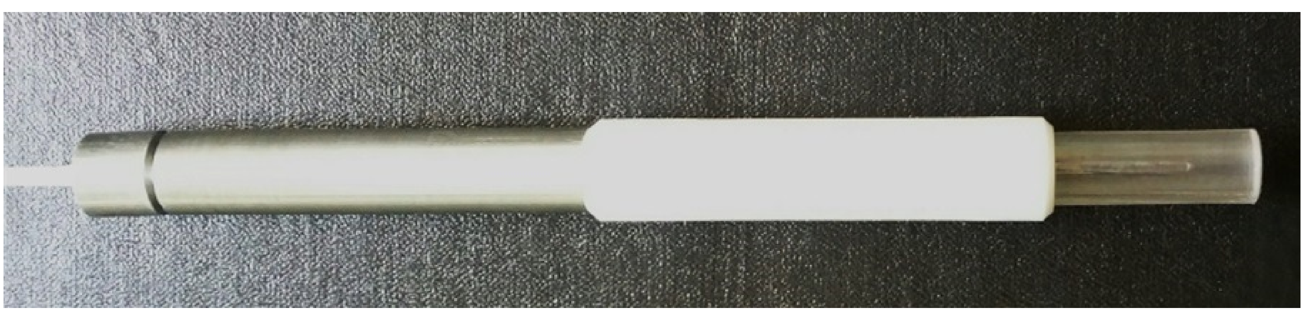

Figure 4. An immersion-type sapphire cryodestructor combining with laser heating and optical diagnosis of tissue.

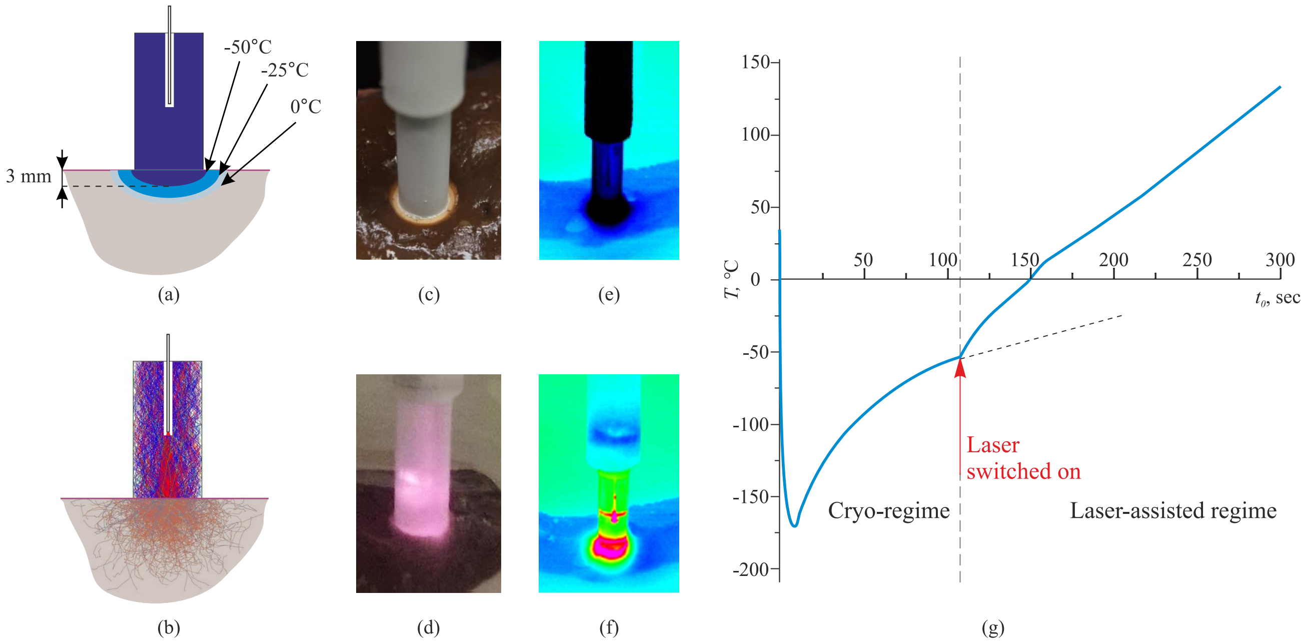

Figure 5. Results of the sapphire cryoapplicator use for the cryosurgery of the liver tissue *in vitro*: (a) a schematic representation of the tissue cryodestruction; (b) results of the Monte-Carlo simulations of the tissue exposure to the laser radiation through the sapphire cryotip; (c, d) photos illustrating the cryodestruction and laser exposure of tissues; (e, f) thermal images (obtained by the infrared camera FLIR Cedip) illustrating the cryodestruction and the laser exposure of tissues; (g) an evolution of the temperature at the sapphire – tissue interface, which was measured experimentally using the copper-constantan thermocouple and illustrates the two regimes of cryodestruction – i.e. the ordinary and laser-assisted ones.

4. CONCLUSION

In this paper, we have proposed the cryoapplicators based on the EFG- and NCS-grown sapphire shaped crystals. They allow for combining the cryodestruction with the laser control of the thermal regimes of cryosurgery and the optical diagnosis of the freezing depth. In order to justify an efficiency of the proposed sapphire cryoapplicators, we have applied them for the cryodestruction of tissues *in vitro*.

ACKNOWLEDGMENTS

The work was supported by the Russian Foundation for Basic Research (RFBR), Projects # 17-08-00803 and # 17-38-80057. VVT was supported by the Ministry of Education and Science of the Russian Federation, Grant No. 17.1223.2017/AP.

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