

A Temperature Stabilization Device for Local Hyperthermia in Cancer Treatment

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Abstract: There are a lot of devices for local hyperthermia in oncology treatment. As usual for local hyperthermia are used very expensive and high power devices based on the using of high frequency or ultrasound. But high frequency is very harmful for patients and medical staff. In addition, high frequency devices for local hyperthermia have a lot of serious shortcomings. This very important and difficult problem can be solved by developed special device for temperature stabilization. This device is very small, low energy, cheap and based on using of harmless direct current. So, the device can be used for the innovative method of cancer treatment not only in large special clinics and research centers but in small clinics and polyclinics too.

Key words: Hyperthermia • Control system • Temperature stabilization • Oncology

INTRODUCTION

The using of hyperthermia in cancer treatment is known for thousands years. The first attempts to use high temperature were made by Hippocrates in 4th century BC [1]. He used red-hot iron to cauterize surface cancer tumors. Such long period of using of high temperature causes the large quantity of different devices for hyperthermia [2].

Local hyperthermia is the method when only the tumor is heating. It is the most progressive method. This method doesn't damage the health cells. There are a lot of different devices for local hyperthermia in the world. The base of these devices is the using of high frequency or ultrasound [3-5]. High frequency can cause a lot of different diseases in patients and in medical staff too. In addition, high frequency devices can heat only surface and subsurface tumors (3-5 cm from the skin). The third shortcoming of them is impossibility of high precision control of temperature level. The fourth shortcoming is the necessity of using of temperature probes to know the current temperature. And, at last, high frequency devices for local hyperthermia are very large, high power and very expensive [6, 7].

So, the aim of the work was to produce the device for controlled local hyperthermia that can eliminate all these shortcomings and have high efficiency simultaneously. The second aim was to make experiments to test the accuracy of the device and to know how the device stabilizes the temperature at the desired level.

Hyperthermia Researches in the World: There are a lot of researches in hyperthermia in the world. Some countries even have special hyperthermia research institutes. In Russia hyperthermia researches are carrying out too. One of the famous Russian researchers in this sphere is Devyatkov N. He was the creator of well known Russian hyperthermia devices "Yakhta" ("Yacht"). There are some generations of this device. And all of them use microwaves (2450 MHz) [6]. So it is possible to use them only for surface tumors. "Yakhta" devices can be used for deeper tumors only with special emitters with very large size (like human body). So, these devices and these emitters are very expensive.

Foreign devices for local hyperthermia are similar to Russian and use microwaves (2450-3000 MHz) or UHF (4-50 MHz). The main difference of foreign devices in compare with Russian is the wider using of computer

technologies. There are some popular foreign devices for local hyperthermia-BSD (BSD-500, BSD-1000 and BSD-2000), Lund-Buchler (4010), Bruker (Hylcar II), Yamamoto Vinyter (Thermotron-RF8), Celsius and so on. Also there are special devices for treating one organ (for example, prostate), such as Prostatherm, Hypertherm ET-100, Prostate Machine etc. [8].

There is another kind of devices for local hyperthermia. These devices instead of external microwaves use needle heaters for transfer microwaves to the deeper tissues. Such method of local hyperthermia is very popular today. This is due to the fact that this method gives the opportunity to transfer heat to deep tissues that significantly expands the sphere of using of local hyperthermia. This kind of devices includes such device as "Vulcan" ("Volcano"), developed in Russia (Nizhny Novgorod). In according to this method suspension of iron (with iron particles size of 0.7 microns) injects into the tumor and then the high frequency (13.56 MHz) heating applies by invasion needle electrodes both around and into the tumor. Also temperature probes are injected into the tumor [1, 9-10].

Using of suspension of iron helps to focus microwaves. But injection of such suspensions is very dangerous. It may cause such complications as aseptic tumor necrosis, abscess, phlegmon at the place of injection, serious intoxication, skin burn with cosmetic defects and so on [1].

The "Vulcan" device can be used without suspension of iron. In this case it will be the possibility to treat deep tissues and it will be possible to get the uniform temperature spread in the heating area due to the injection of needle electrodes. However the injection of needle electrodes and temperature probes into the tumor significantly increase the risk of metastasis. In addition, all shortcomings of microwave hyperthermia are present.

There are also devices for high frequency thermo destruction (destruction of tissues by using the high temperature). This method implies the conversion of high frequency energy, supplied to the center of the tumor by needle electrode, to the thermal energy [11, 12]. In this case high frequency (375 kHz) electric circuit including tumor tissue is formed. As result the temperature inside tumor increases to 56 - 100 °C with necrosis forming. This method is realized by generator Elektrom[®] 106 HETT by Berchtold GmbH and Co Tuttlingen (Germany).

There is one more method-using the invasion of needle electrodes in the heating area during the surgery under the control of ultrasound [3]. In this case the system of radio frequency produced by Radio

Therapeutics Corp. (USA) is applied. It is necessary to say that unipolar electrode is invaded in tumor and indifferent electrode is attached to the skin of the patient. If tumor is small (less than 3.0 cm in diameter) then electrode is invaded in the center of tumor. If tumor is larger, then some electrodes are invaded in different points around the tumor.

One more variant of devices for microwave local hyperthermia implies a preliminary injection of heat transfer agent in tissues through the needle electrode and then the high frequency current will be supplied. As heat transfer agent they use distilled water. The heating is carried out to the temperature 100-110 °C by high frequency current. Electrodes are bipolar, made from two isolated hollow metallic needles. They have built-in temperature probes and system for heat transfer agent supply. External needles have special holes for heat transfer agent supplying to the tissues [13].

So, we can see that all known devices for local hyperthermia with using needle electrodes use body tissues between electrodes as conductive environment, as part of the electric circuit. It may cause the negative impact at interstitial and intercellular structures-violation of the permeability of cell membranes, the negative effect on the nerves, the effects of electrolysis and the destruction of cellular elements. In addition all these methods require the invasion of electrodes into the tumor. It may cause the metastasis growth. Moreover the last device requires heating to 100-110 °C and it is extreme temperature not only for cancer cells but for healthy tissues too. This causes an excessive loss of healthy cells and will also adversely affect the healing process in action area.

The second kinds of devices for local hyperthermia are devices based on the ultrasound. Despite the fact that mechanism of action of ultrasonic waves is not only heat, but a combination of heat, mechanical and physic and chemical factors, these settings need to be addressed, because hyperthermia plays an important role in their action.

One of such devices is Sonotherm[®] 1000 produced by Labthermics Technologies (USA). It can treat tumors located at the depth of 8 sm. The special multi-sectored electrode can increase the square of heating area to 15x15 sm. Different sectors of electrode give the opportunity to control all of them in different ways. This device uses two different frequencies-for surface (less than 3 sm. from the skin, 3.4 MHz) and subsurface (from 3 to 8 sm. from the skin, 1 MHz) tumors [4].

For ultrasound local hyperthermia are more often used devices where catheters for natural holes are used. The main reason of this fact is that the first problem for ultrasound local hyperthermia is the problem of deep tumors and focusing of waves (like microwave local hyperthermia). Although in contrast to microwaves the focusing of the ultrasound waves is complicated not by their dispersion from applicator but by irregularity of their reflection from the boundaries between different layers of tissues. The using of catheters let to provide the supplying of heater to the deep tumors in natural body cavities. This method may be useful in treatment of patients with urinary system tumors of some localization, intestinal tumors, tumors of respiratory system and some other tumors. The example of devices for ultrasound local hyperthermia with using of catheters heaters is Ablatherm® HIFU of French EDAP TMS for treatment of prostate tumors [5].

So, the devices for ultrasound local hyperthermia are used only for treatment of surface and subsurface tumors or tumors in natural cavities of human body (by using heating catheters).

After the review of known devices for local hyperthermia you can see that all of them are based on the high frequency or ultrasound waves. Both of them have a lot of limitations in the use and a lot of shortcomings-very serious shortcomings, that may be the cause of non-using of local hyperthermia method on the whole. So, the main idea for the work was to develop the absolutely new kind of the device for local hyperthermia.

The New Device for Temperature Stabilization: The device for temperature stabilization ensures the maintenance of temperature on the desired level with high

accuracy. It must ensure the prompt reaction on the difference of temperature from the stabilization level less than 0.1 °C. The proposed device is high precision due to its functional scheme (Figure 1 for details).

TR-transistor regulator; NH-needle heater;
HE-heating element; DA-differential amplifier

The device for temperature stabilization in living tissues is based on the Wheatstone bridge that consists of 2 fixed resistors (R_1 , R_2), variable resistor (R_3) and resistor R_T with resistance that depends of surrounding tissues temperature. The heating element (HE) of needle heater (NH) acts as resistor R_T . The principle of Wheatstone bridge is that if you change the resistance in one of its branches there is the voltage difference between its two branches. This difference is going to the entrance of differential amplifier (DA), amplifies by it with necessary amplification factor (K).

Amplified signal goes to the transistor regulator (TR) and change the level of voltage (U_m) that supplies the Wheatstone bridge and, of course, the heating element. I.e. if the temperature of heating element will increase, then the supply voltage will decrease and if the temperature of heating element will decrease, then the supply voltage will increase. The state of equilibrium will be achieved when the power dissipated in the heating element will be equal to the amount of heat, dissipated by blood flow, provided that the environment heated to the predetermined temperature.

Wheatstone bridge resistances are selected in such a way as to ensure the distribution of power between the left and right branches. In our case, the distribution is 1:10, i.e., most of the power sent to the branch in which

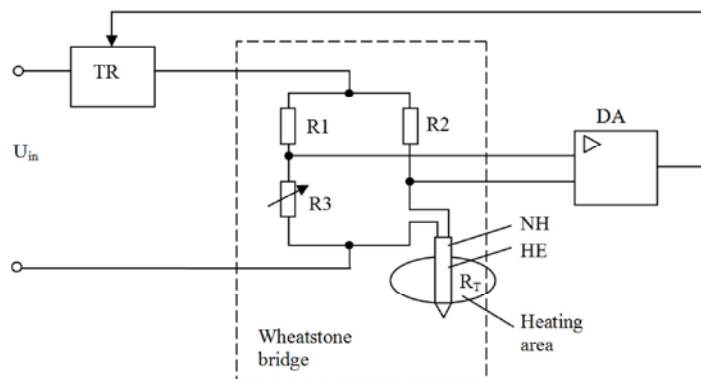


Fig. 1: The functional scheme of the device for temperature stabilization
TR - transistor regulator; NH - needle heater;
HE - heating element; DA - differential amplifier

the heating element is. This ratio provides a resistance ratio of capacity allocated to the right and left branches, as 1:100. As a result, at the heating element is allocated almost all the power supplied to the bridge, which provides a good degree of accuracy and heating.

A feature of this scheme is that when the temperature of heating element changes, its resistance changes too, thereby changing the error signal that is taken from the branches of the bridge. The using of Wheatstone bridge gives the opportunity not to control the temperature but to control the resistance. It is easier to realize it in techniques. Any metal has so called "the temperature coefficient of resistance" (TCR). TCR-is the dependence of the resistivity from the temperature. TCR may be positive (the increase of temperature causes the increase of resistance) and negative (the increase of temperature causes the decrease of resistance). So, we can, having got the chart of TCR for heating element material, determine the resistance at any temperature. It only remains to adjust the Wheatstone bridge in such a way that he carried out the stabilization of the resistance of heating element at the required level. This required level of the temperature will be adjusted by the variable resistor (R3) that will set the potential in the left branch of the bridge.

RESULTS AND DISCUSSION

It was necessary to test all parameters of the device for controlled local hyperthermia and to know how it works in live organism. So it was made a lot of different experiments. You can see the device for temperature stabilization at Figure 2. All experiments were produced using this device.

The accuracy of the device depends of two parameters. First of all, it is the accuracy of calibration. It means we must be sure that the temperature of calibration of needle heaters is absolutely correct. At second, it is the speed of system reaction at the situation when the temperature changes at the very small value-less than 0.1°C.

The results of experiments that give us possibility to check both parameters are shown in Table 1.

You can see in Table 1 that both the first and stabile signals are detected when the temperature changed on less than 0.1 °C. And it is important that such accuracy of temperature stabilization took place both at nominal voltage (5 V) and at 10 % less voltage (4.5 V). So, this table confirms that our device carrying the high precision stabilization of the temperature at the desired level.

To check the work of the temperature stabilization device in the biological tissues the special experiments (on meat) were done. During these experiments it was the task to provide the temperature stabilization at 43-44 °C. In addition, we had to reach this temperature level in 15-20 minutes. Also it was necessary to establish that the device makes the minimal action at healthy cells. The results of these experiments are shown at Figure 3. You can see that temperature stabilization is at 43 - 43.5 °C and the time of reaching of this level is 16-18 minutes. Also you see that outside area (outside the circle of needle heaters) is practically not differs from environmental temperature (i.e. the living tissues temperature without heating).

Probe 1-in the center of heating area, probe 2-28 mm from the center (outside the circle), $T_{\text{Environment}}$ -environmental temperature (tissues far from heating area), T_{Desired} -desired level of temperature stabilization.



Fig. 2. The device for temperature stabilization

Table 1: The results of experiments for accuracy research

Calibration accuracy checking		Stabilization accuracy checking		
Calibration temperature, °C	Calibration temperature deviation, °C	Supply voltage, V	Temperature changing that causes the first signals, °C	Temperature changing that causes stabile signals, °C
47	± 0.1	5	0.02-0.03	0.04-0.05
		4.5	0.03-0.04	0.05-0.06

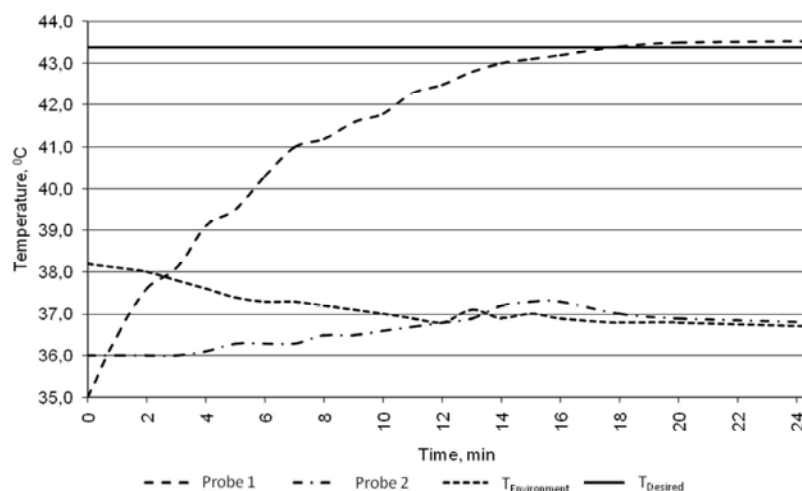


Fig. 3: The results of experiments on the temperature stabilization (heating area-20 mm in diameter, heaters temperature-45 °C)

CONCLUSION

There are a lot of different devices for local hyperthermia in the world. But no one of them can treat people without any harm for patient and/or for medical staff. So, it was very important to develop the new kind of the temperature stabilization devices. And in this paper such device was shown. It can stabilize temperature at the desired level with high accuracy. And it has the direct current as the base of its work. So, this device has no any shortcomings which are in UHF and ultrasound devices. The new device can transfer heating to any deep tumors without stimulating of cancer and metastasis growth.

Findings: So, the new temperature stabilization device for local hyperthermia in cancer treatment was presented in this paper. This device is high precision and effective for any deep tumors but has no any shortcomings which are in any other local hyperthermia devices.

Such technical parameters of the device as harmless direct current as the base of it, small size and low power and, in addition, cheapness (in compare with known devices) will give the possibility for small clinics and polyclinics (not only large research centers and special oncology clinics) to purchase the device for temperature stabilization and to treat more people than it is possible now.

REFERENCES

1. Hyperthermia methods in oncology. Date Views: 10.01.2014 www.k-test.ru/index.php?rid=3 and [pid=6](http://www.k-test.ru/index.php?pid=6).

2. Pakhmurin, D.O., 2012. Electronic devices for temperature control in non-closed amount of living tissue, PhD thesis, Tomsk State Univ. of Control Systems and Radioelectronics, Tomsk, Russia.
3. Curiey, S.A., *et al.*, 1999. Radiofrequency Ablation of Unresectable Primary and Metastatic Hepatic Malignances. Results in 123 Patients. *Annals of surgery*, 230(1): 2-3.
4. Labthermics Technologies, Inc. Date Views: 18.07.2010 www.labthermics.com.
5. EDAP TMS-Global leader in therapeutic ultrasound. Date Views: 10.01.2014 www.edap-tms.com.
6. Konoplyannikov, A.G., A.N. Dedenkov and O.K. Kurpeshev, 1983. Local hyperthermia in radiotherapy of cancer. Moscow, pp: 60.
7. Khitrov, Yu. A. and V.N. Makarov, 2008. The method of high temperature destroying of biological tissue and the device for its realization. Patent # 2317793 RU.
8. Konoplyannikov, A.G., 1991. Electromagnetic hyperthermia (high frequency and UHF) in treatment of tumors and non-tumor diseases. *Physical Medicine*, 1: 1-11.
9. Karev, I.D., B.K. Dolotov, E.L. Belousov, V.V. Shkarin A.N. Napalkov and I. Savin, Yu, 1993. Method of cancer treatment and device for its realization. Patent # 93031981 RU.
10. Terentev, I.G., I.S. Shumskaya, V.I. Kirilin, S.S. Kuznetsov and S.P. Petyashina, 2002. Local HF-hyperthermia with current conducting liquor in combined treatment of mammilla cancer. *Nizhegorodskiy Medical Journal*, 1: 54-57.

11. Fedorov, V.D. *et al.*, 2001. The first attempt of clinical applying of controlled by ultrasound intra surgery through skin high frequency treatment of metastatic liver tumors by needle electrodes. Actual questions of diagnostics and surgery treatment of metastatic liver tumors, pp: 171-172.
12. Shaposhnikov, A.V., A.A. Perfilov, Yu. N. Bordyushkov and E.M. Nepomnyashchaya, 2004. The method of treatment of unresectable primary and metastatic liver tumors. Patent # 2231991 RU.
13. Khitrov, Yu. A. and V.N. Makarov, 2008. The method of high temperature destroying of biological tissue and the device for its realization. Patent # 2317793 RU.