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Controlled Local Hyperthermia and Magnetic Hyperthermia for the Treatment Cancer Deseases

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ABSTRACT

Average size of hematite and magnetite micro and nano powders and poly dispersity index, zeta potential and distribution of particles were studied. Analysis showed that average size of the obtained particles for magnetite is 740.9 nm, for hematite ultra-dispersive particles – 30-100 nm. Alternate current feed source was created for hyperthermia. Proceeding from the requirements of the objectives the U type MnZn material magneto conductors were selected, in which 10.0 and 8.0 mm width gaps were cut and glass test tubes with magnetite or hematite suspensions were placed in them. Series of experiments at various field intensity and frequencies showed that for efficient magnetic hyperthermia therapy more powerful device was needed with frequency of up to 10 Mega Hertz to achieve the temperature -42-45°C necessary for full activation of Neel and Brown mechanisms in particles.

At the next stage, on the basis of experimental material the anticancer mono-therapeutic effect of hyperthermia and its adjuvant action in poly chemotherapeutic treatment was presented by the use of a device created by us – "Lezi". As a result of the experiment it was shown that in all animals (outbred albino mice, 3 months old) inhibition of cancer growth was fixed and intratumoral necrosis developed, while after 7 and 10 sessions tumors were ulcerated, which refers to positive effect of the experiment (Conclusion of Pathologic anatomical Laboratory "PATGEO", Tbilisi, Georgia).

High anti-blastoma effect innovative technology was developed. Apparatus worked from 2019 on patients in oncological clinic "INTEGRA" Kutaisi for treating by "Cancerthermia" method. Received high results. The anti-cancer mono therapeutic effect and adjuvant action was proved in cancer polychemiotherapy. Creation of innovative technology of locally controlled "Cancerthermia" for treating patients.

Keywords

Magnetic hyperthermia, Nanopowder, Malignant cancer, Necrosis, Ulceration, Controlled local hyperthermia, "Cacerthermia".

Introduction

It is known that malignant cancers consist of cancer cells, which differ from normal ones by uncontrolled and unlimited propagation and growth of cells. Therefore, intensity of metabolic processes in malignancies and, correspondingly, energetic requirements are higher than in common healthy tissues. Taking into consideration this factor, it is perspective to use chemical and biophysical effects on cancer tissues and its neighboring tissues, which in definite time period will exhaust energetic potential of degenerated cells, will result in denaturation (death) of their proteins and will preserve viability of healthy cells.

Such biophysical impact might be the local hyperthermia (42-45 °C).

Cancer cells die at about 43° C, since delivery of oxygen via blood vessels is insufficient, while normal cells are not injured even at higher temperature. Alongside with it, cancer is heated easier than

normal tissues around it, since blood vessels and nervous systems are less developed in cancer [1-3].

Research strategy is Therapy of voluntary patients in the clinic by the method "Cancerthermia" created at the Center of Bionanoceramic and Nanocomposites Material Science Center of Georgian Technical University (GTU) by the use of Clinical apparatuses "LEZI-1" Innovation and uniqueness of the technology is that, on the base of experimental material, for the first time in Georgia therapeutic effect and adjuvant action of anti-cancer mono-therapeutic treatment was presented in cancer's polychemiotherapy.

Ceramic microspheres for cancer radiotherapy $Y_2O_3 – Al_2O_3 – SiO_2$ glass microspheres

In 1987 Hyatt and Day [4] and Erbe and Day [5] proved for the first time that it was possible to use $17Y_2O_3 – 19Al_2O_3 –64\ SiO_2$ (mol%) 20-30 μM diameter glass microspheres for *in situ* irradiation of cancer. In this glass Yttrium-89 (^{89}Y) is nonradioactive isotope, which is found in nature at 100%, but neutron irradiation results in activation of ^{89}Y, which results in creation of β-irradiating ^{90}Y, half-life of which equals to 64.1 hr. When these 20-30 μM diameter radioactive glass microspheres are injected into organism (e.g. liver cancer) they fall into narrow blood vessels of cancer and block delivery of nutrients. Alongside with it, it gives high-ionized β -rays acting at short distances. β-ray does not affect other chemical elements and it has short, 2.5 mm penetration range into live tissue and thus is not dangerous for healthy tissues. These microspheres are characterized by high chemical durability and therefore the radioactive ^{90}Y microsphere stays in diseased body and doesn't affect surrounding healthy tissues. Radioactivity of ^{90}Y at neutron irradiation [6] decreases to insignificant level in 21 days; therefore, microspheres lose activity after treatment of cancer. They are used already clinically for liver cancer therapy in Canada, USA and China. They are used in clinical experiments for treatment of affected kidney and spleen and in cinoectomy irradiation of arthritis joints [7-20].

Ceramic microspheres for cancer hyperthermia, ferromagnetic glass ceramics

Currently lithium ferrite ($LiFe_5O_8$) containing glass ceramic in hematite (α-F_2O_3) bio-compatible matrix and SiO_2-P_2O_5 glass phase [21-27], magnetite (F_3O_4) in β-volastonite (β-$CaSiO_3$) matrix and CaO-SiO_2-B_2O_3-P_2O_5 glass phase [28-35], α-Fe_2O_3 [36], in Fe_3O_4 B_2O_3 -free CaO-SiO_2-P_2O_5 glass phase [37] and zinc-iron ferrite in CaO-SiO_2 glass phase [38] are developed as thermo grain to be used in hyperthermia. Thus, e.g. glass ceramic, that contains F_3O_4 in β-$CaSiO_3$ matrix and CaO-SiO_2-B_2O_3-P_2O_5 glass phase was efficient [29-31] in destruction of cancer cells implanted in rabbit femoral bone, when it was introduced in the pin-form into brain channel and [36] was placed in alternate magnetic field [33]. But such glass-ceramic pins can't be used clinically, since cancer cells can be scattered around normal cells and injection of glass-ceramic pins can result in cancer metastasis. 20-30 μM diameter ferromagnetic microspheres might be used for local heating of cancer through loss of hysteresis by ferromagnetic materials, without initiation of cancer metastasis. Microspheres can be introduced into cancer via blood vessels [39] and then place it in alternate magnetic field. But up to now, 20-30 μM size microspheres are not obtained and they have not revealed high heat formation capacity. Currently precise mechanism of hyperthermia for cancer therapy is not known. Unknown is the size of magnetite or hematite particles too. There are no data in special references about it.

Index of morbidity and lethality conditioned by melignancies in the whole world is increasing permanently. Early diagnostics is rather difficult and majority of patients address hospitals because of generalized cancers (III-IV stages), when they need combined surgical, radiation and drug therapy and complex treatment. Number of patients who address physician-oncologists with manifestation of clinical signs and various metabolic derangements inherent to complicated cancer processes has increased.

Development of new methods of treatment of melignancies is the most urgent task of oncology Inculcation of drugs and methods of treatment possessing positive effects which are proved by experimental and clinical studies –into clinical practice is a forward step in the sphere of treatment of oncologic patients.

Goal and objectives of hyperthermal studies

The present research pursues improvement of modern and recent results in the sphere of treatment of patients suffering from cancer, by the application of hyperthermia on cancer formation.

To achieve this goal we plan to resolve the following objectives:

1. Study of anticancer therapeutic effect on experimental cancers'
2. Determination of adjuvant anticancer effect of hyperthermia in experiment, in combination with poly-chemotherapy.
3. Study of various regimes of hyperthermia considering immediate and recent results.

Experimental

To implement the first stage works, first of all, we'll take X-ray of the used magnetite powder and hematite nano-particles obtained on the rotation kathode device created by us; (Figure 1 and Figure 2)

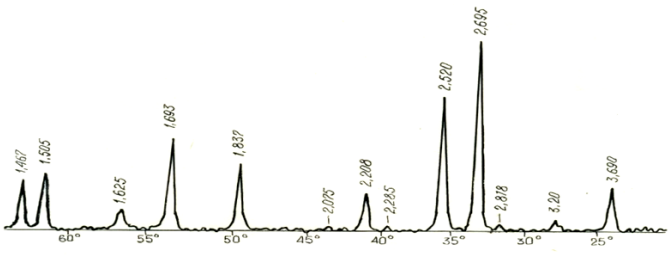


Figure 1: X-Ray of the obtained (α-Fe_2O_3) hematite nanopowder.

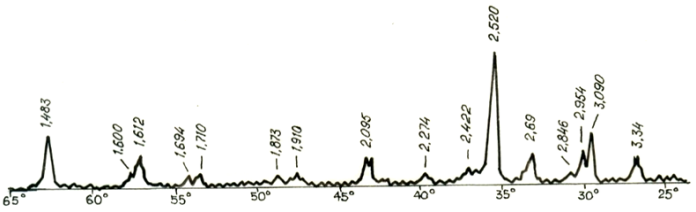


Figure 2: X-Ray of the used magnetite (Fe_3O_4) micropowder.

As is seen from the X-ray analysis magnetite consists mainly of Fe_3O_4, d_{hkl}=2,954; 1,520; 2,095; 1,710; 1,612; 1,483Å, hematite d_{hkl}=2,690; 2,520; 2,422; 1,710; 1,694; 1,600 Å, traces of $CaCO_3$ d_{hkl}=3,030; 1,910; 1,873 and traces of SiO_2, but the main mass is magnetite, therefore powder is of dark black color.

The obtained hematite powder is red, and the mass completely consists of α-Fe_2O_3. With "Nanophox" device –Clausthal-Zellerfeld, Germany - accumulation curve of hematite particle distribution and particle density-normal Gauss distribution was determined (Figure 3 and 4). From Figures is shown, that in powder the particles (agglomerate) with sizes till 300 nm are 62-63%. The "Nanophox" device fixd also the agglomerated nanopowder. Figure 5 shows graphical representation of analysis of hematite powder stability. Figure 6 shows the rotation cathode device created by us (Patent, receiving methode-registration number 11731, 15.03.2010. Georgian National Patent Center "SAQPATENTI").

After phase analysis the physical properties of magnetite powder were studied on the apparatus "Nanosizer" of Great Britain origin (in Germany, Clausthal-Zellerfeld, Institute of Steine und Erden). Powder was screened through # 0063-8270 mesh sieve in advance.

Intensity on the offered Figures is that of the transmitted laser ray, Width - is a peak width and shows the particle distribution according to dimensions. The narrower a peak, the more homogeneous is spreading.

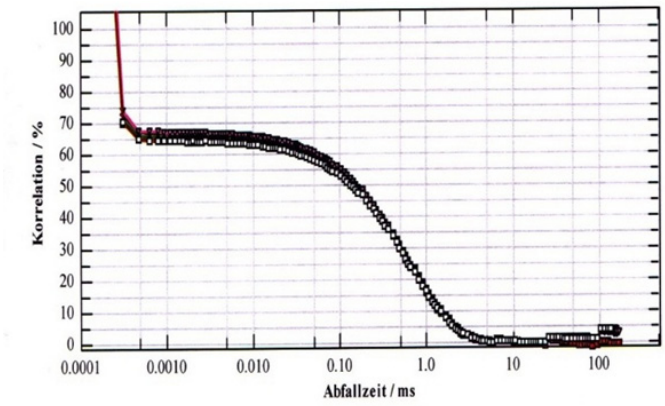


Figure 5: offers graphical expression of analysis of powder stability. In the process of Analysis powder revealed homogeneity, equal distribution according to sizes and correspondingly, good stability.

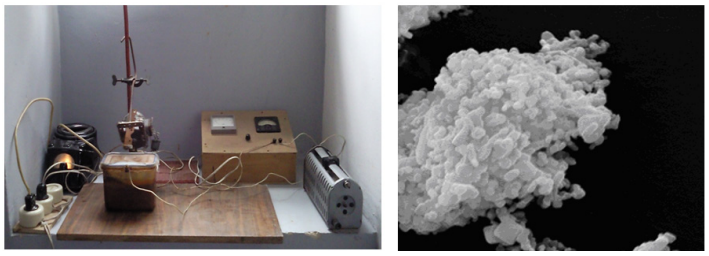


Figure 6: The rotation cathode device for receiving of hematite nanopowders and scanning electron-microscopy representation of hematite agglomeration. Average size of the particle 30-100 nm.

Particle characterization is based on the average size and polydispersity index Pdl. If its value is within 0,1-0,5 the suspension is of good polydispersity.

Zeta potential is the potential of diffuse layer of a particle, which is in the solvent. If the value of Zeta-potential is within 30mv +30mv, such particle has a tendency towards aggregation.

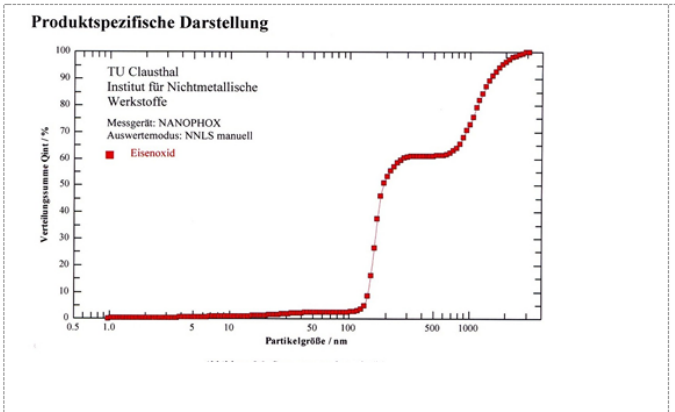


Figure 3: The curve of the particle distribution of the hematite nanopowder.

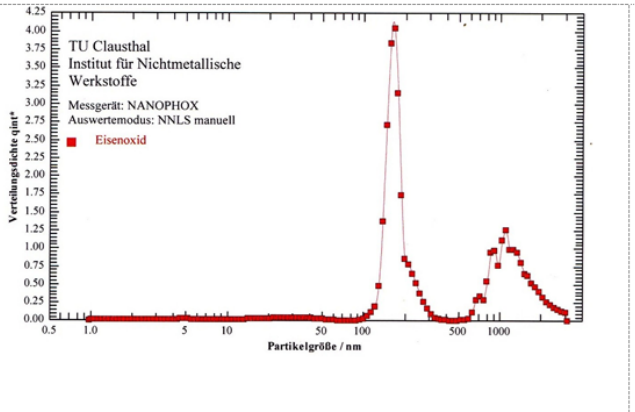


Figure 4: The compactness of the hematite nanopowder.

According to the analysis the sizes of the obtained particles are redistributed mainly in two ranges/bands. Approximately 93% of particles are of 200-1000 nm and their average size equals to 478.6 nm. Sizes of approximately 7% of particles are within 3-7 µM. Their average size is 5.41 µM. This should be a result of nanoparticles aggregation. To study the impact of further mechanical treatment on the sizes of the obtained particles, experimental lot was treated in a porcelain cup, for 5 hours, in single-ball vibrating mill.

After grinding in vibrating mill for 5 hours the average particle size is 740.9 nm, polydispersity index - 0.571; big (coarse) 3-7 µM size particles disappeared, general dispersity of particles increased, which conditioned low Zeta –potential - 19.8 mv. This refers to a tendency of this dispersity powder towards aggregation.

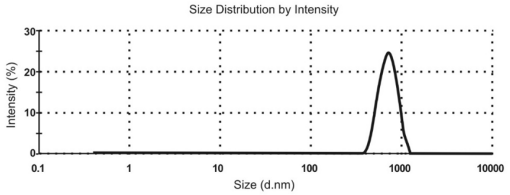


Figure 7: Analysis of powder ground in vibrating mill for 5 hours. Dispersant – water.

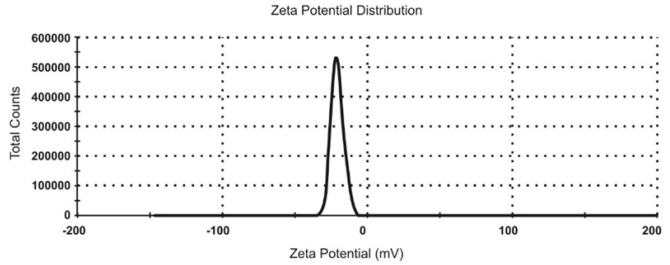


Figure 8: Zeta –potential of powder ground in vibrating mill for 5 hrs. Dispersant – water.

The present research aimed to create a device for hyperthermia. Original, alternate current feed source (Figure 9) was created for application of method of hyperthermia, to achieve thermal scattering of magnetic particles [40-42] and to obtain alternate current magnetic field. The device is characterized by the following parameters:

- Output voltage 0 -240 V;
- Current for loading – 10 A (long-term regime);
- Peak load – 12 A;
- Range of alternate current frequency – 20 kHz – 295 kHz
- Frequency alteration load – 1 kHz.

Output voltage value was restricted by the terms stipulated for security observance.
Schematic-construction type parameters of the above stated feed source were experimentally correlated according to the alternate magnetic field intensity level to be created.

Thermocouple was used for temperature measurements (due to small sizes and low inertia) in a set with 3.5-rate digital tester. For elevation of accuracy of this method a tester was calibrated at 45°C.

For measuring of current form, value and frequency we used electron-ray two-channel 1 MHz oscillograph. Dada was taken at 0.1 Ohm 0.1% accuracy shunt inserted in power circuit, at the coil, in succession.

Determination of the necessary level of magnetic field intensity was based on the following experiment: in 10 mm diameter PVC (polyvinylchloride) test tube, in 1 gram distilled water the 1x3 mm size 15 mg thin iron plate was immersed (hereinafter referred as Tube #0). It was considered that at definite approximation, the above stated composition was a version corresponding to 1.5% water solution of the tested powder. Then a tube was placed in various intensity alternate magnetic fields.

Practically all types of toroidal, TD, E, ELP, U standard dimension magnetic conductors were tested.

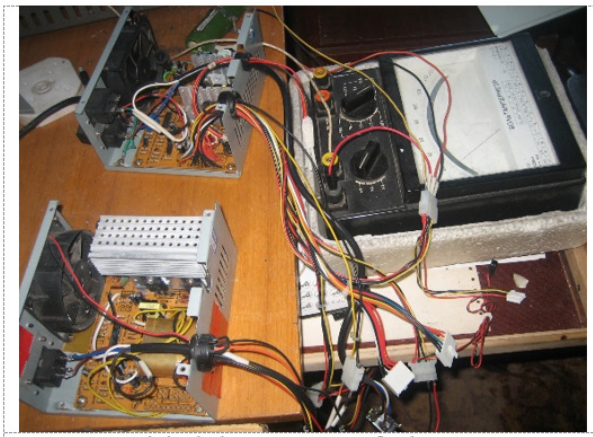


Figure 9: Original alternate current feed source.

Figure 10: Selected magnetic conductor types.

Proceeding from the pursued objectives, after data correlation the preference was given to U type magnetic conductors of MnZn material, of 67/87 electromagnetic properties (Figure 10). To receive the needed dimensions, alongside with the standard magnetic conductors, we used those of needed sizes, which were obtained by corresponding mechanical treatment of ETD34, E42 and E52 standard magnetic conductors.

In the bundle of magnetic conductors various size gaps were cut: 20mm, 16 mm, 12 mm, 10 mm and 8 mm. On the basis of experience acquired in the process of experiments 10.0 mm and 8.0 mm width gaps were given preference as working ones. Similarly, optimal dimensions of magnetic conductors in millimeters were selected:

1. 50 X 50 X 11;
2. 60 X 50 X 12;
3. 40 X 40 – area of magnetic conductor section 32 mm^2;
4. 40 X 30 - area of magnetic conductor section 32 mm^2.

To cover the whole range of 20 kHz-295 kHz frequency electric coils were prepared for every magnetic conductor:

1. 42 windings – 2.0 mm transformer copper conductor;
2. 36 windings - 2.0 mm transformer copper conductor;
3. 34 windings - 2.0 mm transformer copper conductor;
4. 30 windings - 2.0 mm transformer copper conductor;
5. 30 windings - 3 X 0.6 mm transformer copper conductor;
6. 26 windings - 2.0 mm transformer copper conductor;
7. 22 windings - 2.0 mm transformer copper conductor;
8. 18 windings - 1.5 mm^2 section mounting multithread copper conductor;
9. 16 windings -1.5 mm^2 section mounting multithread copper conductor;
10. 12 windings -1.5 mm^2 section mounting multithread copper conductor;

Magnetic conductors prepared by us together with the above stated alternate current feed source enabled us to carry out sets of experiments at various field intensity and frequency.

#1 and #2, that is 5% and 10% suspensions were prepared from hematite and magnetite, correspondingly. From 8 mm diameter glass pipe the tubes were made in which the above referred suspensions were poured (Figure 11).

Initially experiments were conducted at the frequencies: 27.7 kHz, 33.3 kHz, 40.0 kHz, 50.0 kHz, 66.0 kHz, 100.0 kHz, 166.0 kHz, 200.0 kHz, 250.0 kHz and 290.0 kHz.

By variation of voltage coming from power source we fixed 4.0. 5.0, 8.0, 9.0 and 10.0 A current in electric coils. Temperature monitoring was performed in 1 min, 5 min, 10 min and 15 min intervals. Expediency of continuation of experiments in alternate magnetic field of lower than 8.0 A was practically excluded. Similarly, was excluded application of gaps width of which exceeded 10 mm. Magnetic field intensity in 8 mm and 10 mm gaps for magnetic conductors of the above frequencies were obtained: 4200 A/winding, 4000 a/winding 3800 A/winding, 3400 A/winding, 3200 A/winding, 3000 A/winding, 2800 A/winding, 2600 A/winding.

The first series of experiments showed that temperature of solutions in tubes placed in magnetic field (Figure 12) compared to the environment temperature used to increase within 15 minutes only by 8.0-10.0°, inclusive 6-7°, within the first 5 minutes. Tube #0, when placed in analogous intensity field within the first 5 minutes yielded 25-30° increase, inclusive 15-20° in the first minute. Intensity of increase of temperature is directly proportional to magnetic field intensity. In the process of experiments, in gaps, at high magnetic field intensity, significant overheating of magnetic conductors and power winding was observed. According to measurements, temperature on the surface of magnetic conductors at gaps used to increase up to 50-70 ° C during experiments. Therefore, the impact on tubes would have been significant too. A series of experiments was carried out that showed that increase of temperature by 6-7 ° C in 5 min period in tubes was conditioned by thermal effect of magnetic conductor in gaps.

As it was shown by the experiments, more powerful device of 5-10 mega Herz is needed for efficient treatment by magnetic hyperthermia to enable thorough activation of Neel and Brawn mechanisms at the impact of alternate magnetic field on micro- and nanopowders obtained by us. The works in this direction will be continue. We have developed also other method, a new device for hyperthermia therapy and further works were continued at the second stage. Conditionally we called the device "Lezi" (Figure 13). (Georgian Inteligent Privecy National Center "SAQPATENTI". Deponing Certificate 5054. Work: "Control Local Hyperthermia

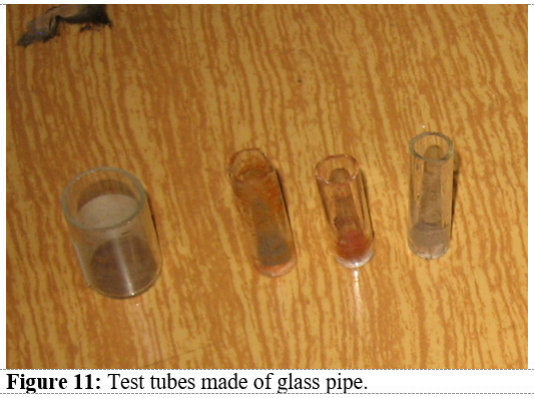


Figure 11: Test tubes made of glass pipe.

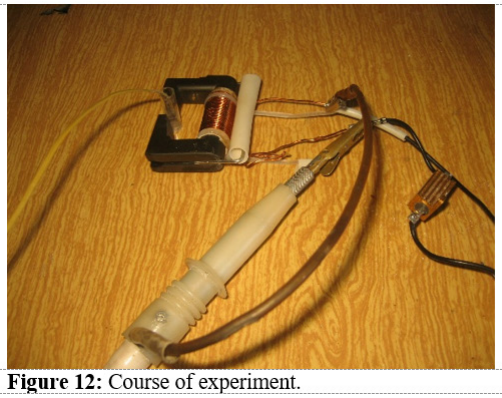


Figure 12: Course of experiment.

and Magnetic Hyperthermia for Therapy of Malignancies").

Figure 13: Device "Lezi" (in the left). Cage with mice (in the right).

Antitumoral effect of hyperthermia in experimental cancers at the treatment by a device "Lezi"

Stage II

Scientific novelty

On the basis of experimental material the anticancer mono-therapeutic effect of hyperthermia and its adjuvant action in polychemotherapeutic treatment was presented for the first time in Georgia. With this in view rational schemes of hyperthermia were developed.

Essence of Research

Materials and Methods

3 months old 18-20 g albino mice (outbred, non-linear) were used in experiments.

After selection for experiments, the mice were kept in vivarium for 10-14 days at quarantine regime, according to sex. Individual protocols were executed for each animal. Animals were kept at similar feeding and care conditions.

Experiments were carried out by the use of cancer strain of Erlich adenocarcinoma. Inoculation of Erlich adenocarcinoma was performed in mices, subcutaneously, in infrascapular region.

Experiments were carried out by the methods widely applied in experimental oncology. The anticancer effect of hyperthermia was evaluated according to cancer growth inhibition, frequency of intratumoral necrosis and changes in the data of animal life prolongation.

The results will be processed by variation statistics methods.

The study was conducted on 18 groups of mice. Here are the typical results:

Obtained results and discussion

Experiments fixed inhibition of cancer growth in the I, III and V animals, while in the II, IV and VI animals, where progressive growth of a size of cancer formation was observed, the so called "intratumoral necrosis" was developed in cancers – necrosis of cancer cells. This, according to our opinion is conditioned by the effect of hyperthermia.

In the second experimental group we again studied anticancer therapeutic effect of hyperthermia. On the first day of the experiment, on 17.04.2024, subcutaneous inoculation of EAT cancer strain was performed. Cancer developed in all three experimental animals.

17.04.2023 - we measured animal cancers (see Table 1, Figure 14). Measurements were performed after every 3 sessions. On 20.04.2024 the first session of hyperthermia was carried out. These sessions were carried out every second day. A device was placed on cancer formation; at the ends of a device 43-45 °C was fixed. Length of hyperthermia manipulation equaled to 30, 40 and 50 min, correspondingly, on I, II and III animals. The first mouse was two-humped. Treatment was performed on the right hump.

After 3 sessions of the experiment it was found that in all three animals inhibition (stopping) of cancer growth was fixed, while the II and III animals revealed development of intratumoral necrosis in cancers (Figure 14). In this case, again, inhibition of cancer growth and intratumoral necrosis were conditioned by the effect of hyperthermia.

In these animals measurements were made after seven sessions. According to Table 2 and visually necrosis and ulceration are observed, which refers to positive effect of the experiment. After ten sessions, again vivid necrosis and ulceration of the tumor was observed, see Figure 15.

Table 1

Animal	Number of sessioins and date of measuring size					
	I 17.04.2023	II 20.04.2023	III 22.04.2023	IV 24.04.2023	VII 30.04.2023	X 09.05.2023
1	8x8x5/10x8x5	8x8x5/10x5x5	10x8x5/8x5x3 (necrosis)	10x8x5/5x5x3 (necrosis)	12x10x8/5x5x3 (necrosis, ulcerarion)	10x10x8/8x8x5 (necrosis, ulceration)
2	10x8x5	10x8x5	8x8x5 (necrosis)	8x6x3 (necrosis)	16x12x5 (necrosis, ulceration)	12x9x5 (necrosis, ulceration)
3	16x14x10	16x14x10	16x14x10 (necrosis)	16x14x5 (necrosis)	17x14x5 (necrosis, clearly expressed ulceration)	21x14x8 (necrosis, clearly expressed ulceration)

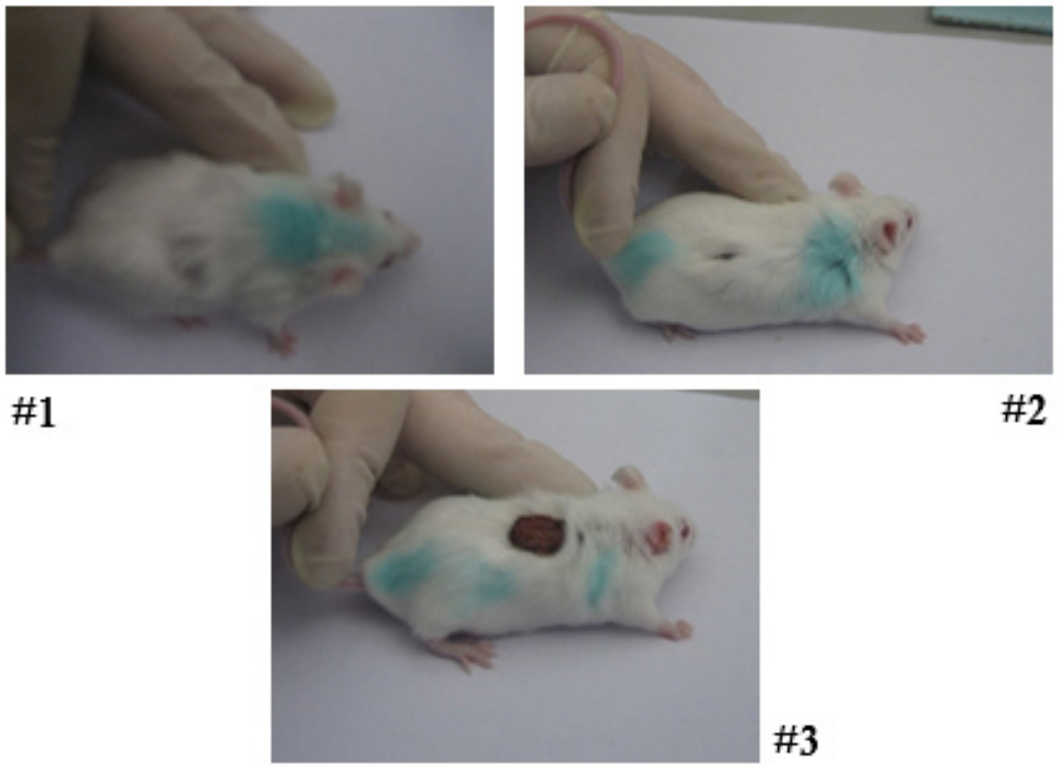


Figure 14: Animals #1, #2 and #3 after 3 sessions. Intratumoral necrosis was observed in the II and III cases. In the I case inhibition of progress of cancer was observed.

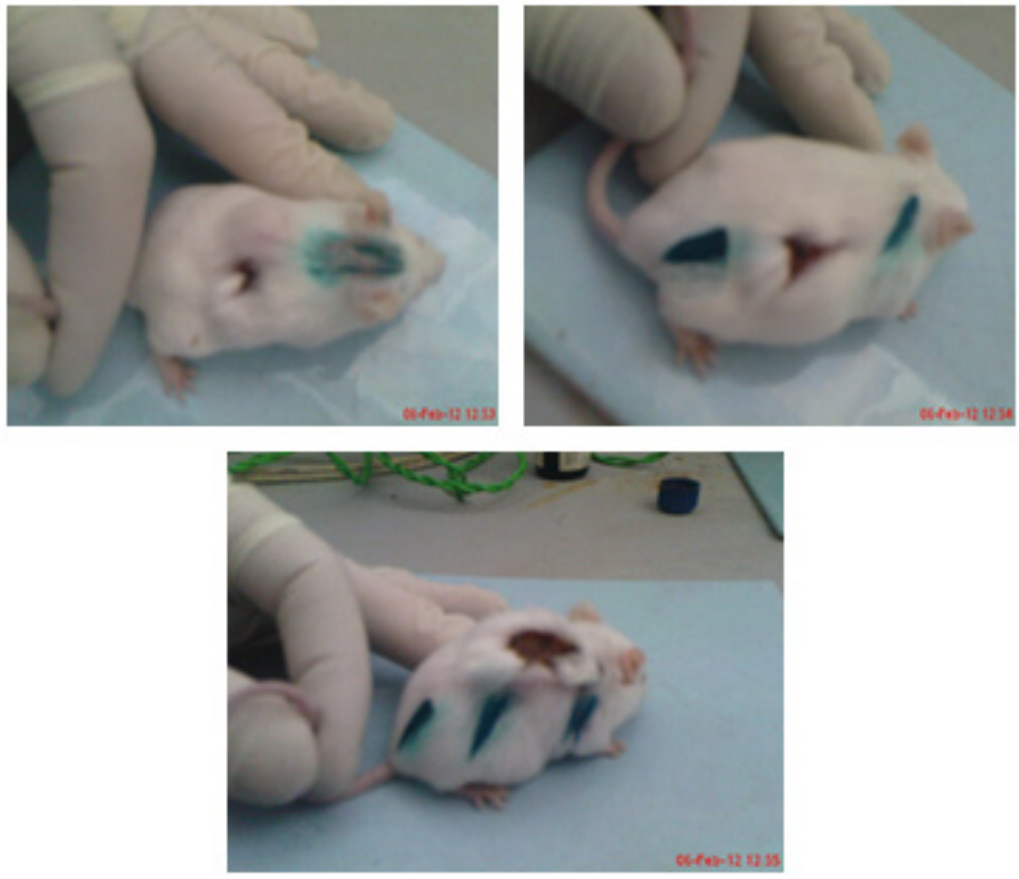
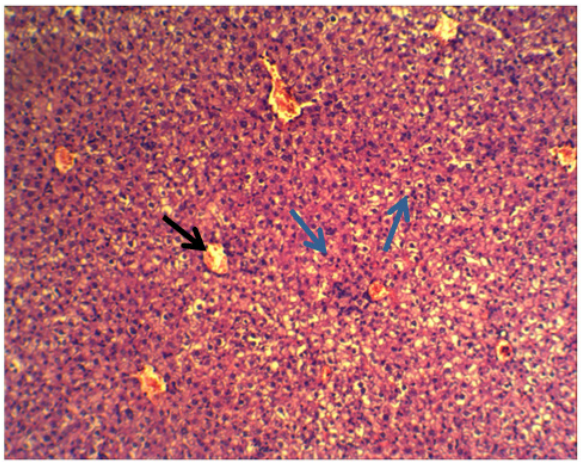


Figure 15: #1. #2 and #3 animals after ten sessions. Ulceration of tumor is fixed. Necrosis is clearly expressed

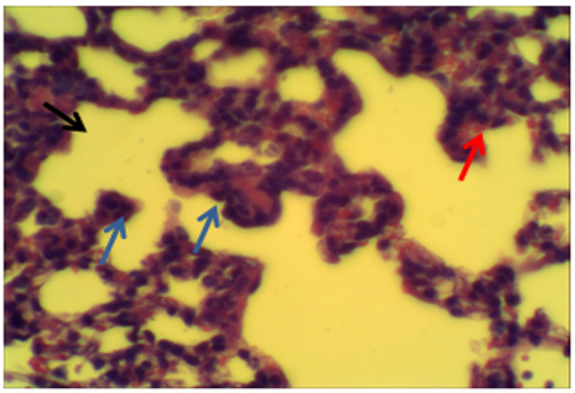
According the next stage of experiments the results show, that After the eighth session necrosis of the whole treated diseased section was apparent and ulceration around the tumor section in all three animals was observed which refers to transition of disease to the phase of recovery. Currently animals are under supervision, they feel themselves well.

There were three or four sessions left before the end of the treatment, but at the suggestion of the oncologists, both animals were euthanized and an analysis of the liver and lungs was performed in the pathological-anatomical laboratory "Pathgeo" to see the possibility of metastatic spread of the tumor to the organs. The analysis with pictures and their description is presented below.



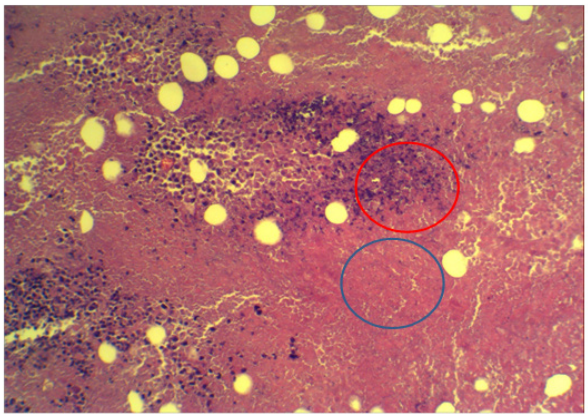
N1 A Liver

Figure 16: The black arrow shows a blood vessel with the presence of erythrocytes in it. The blue arrow shows hepatocytes (liver cells) around the blood vessel. Tumor cells are not detected in the preparati.



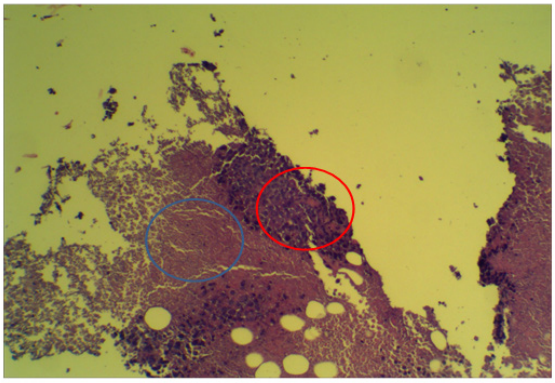
1 A. Lung

Figure 17: Black arrow - shows pulmonary alveoli, blue arrow - first-order alveolocytes, red arrow - erythrocyte. Tumor cells are not detected in this preparation. Accordingly, based on the results of morphological studies, no liver and lung tumor metastases were observed.



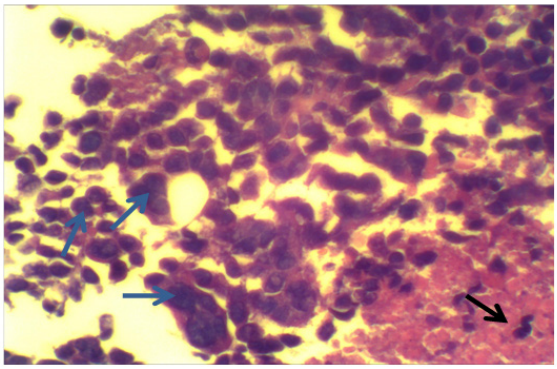
A Tumor

Figure 18: Blue circle - necrotic masses. Red circle - karyorhexis (the process of cell nucleus breakdown). Tumor cells are observed, with pronounced posimorphism, which characterizes Ehrlich adenocarcinoma.



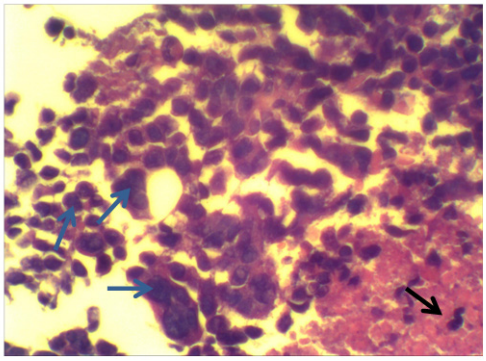
A Tumor

Figure 19: Blue circle - necrotic tissue. Red circle - tumor cell plastids, characterized by pronounced nuclear polymorphism (various).



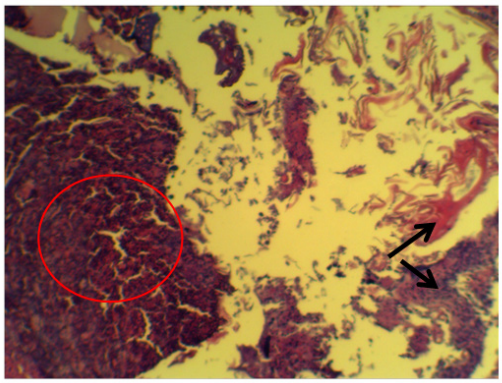
A Tumor

Figure 20: Black arrow - focal necrosis. Blue arrow - tumor cells, characterized by hyperchromic (dark), sharply polymorphic nuclei.



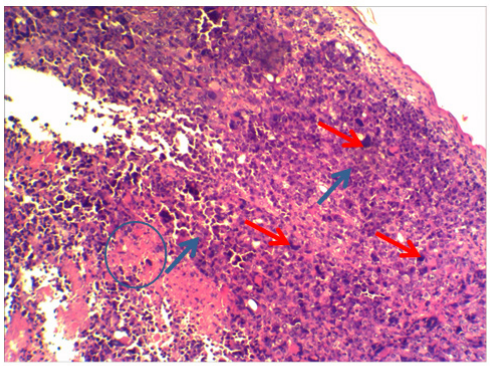
A. Tumor

Figure 21: Black arrow - focal necrosis. Blue arrow - tumor cells, characterized by hyperchromic, sharply polymorphic nuclei.



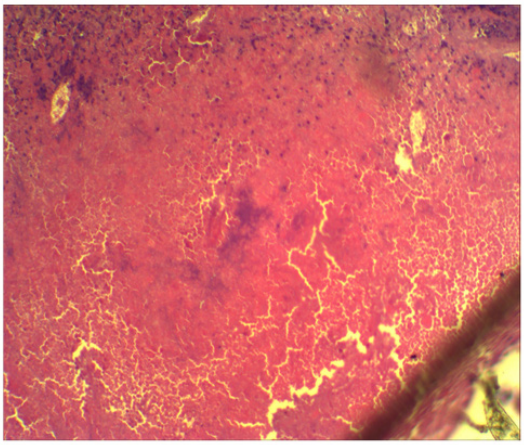
A. Tumor

Figure 22: Black arrow - skin, epidermis, subcutaneous tissue. Red circle - solid proliferates of tumor cells (multiplying cells).



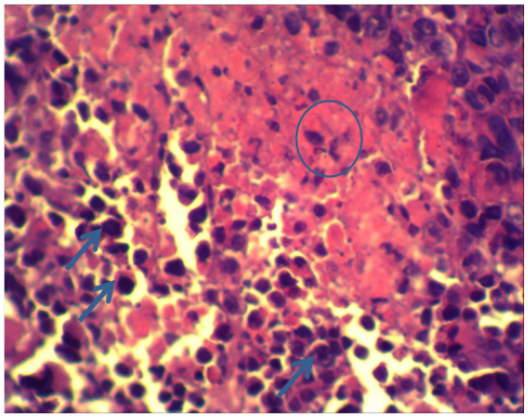
A. Tumor

Figure 23: Blue circle - necrosis center. Blue arrow - tumor cells, characterized by hyperchromic, sharply polymorphic nuclei. Red arrow - so-called. ugly cells.



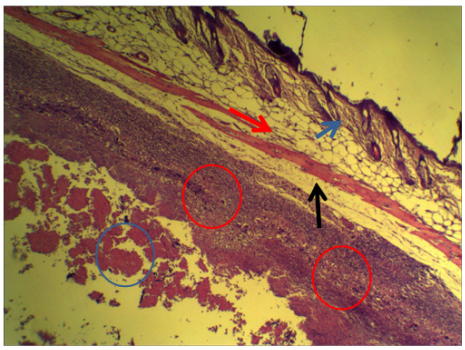
A Tumor

Figure 24: This image shows necrosis.



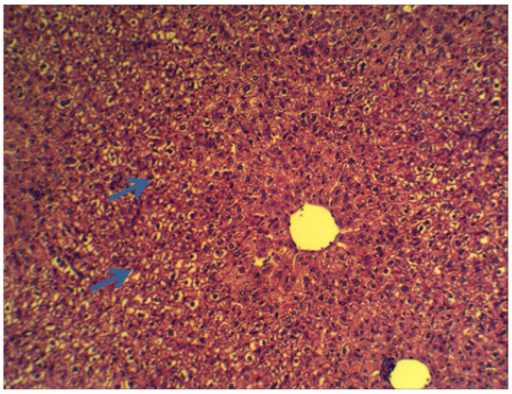
A Tumor

Figure 25: Blue circle - a focus of necrosis. Blue arrow - tumor cells, characterized by hyperchromic, sharply polymorphic nuclei.



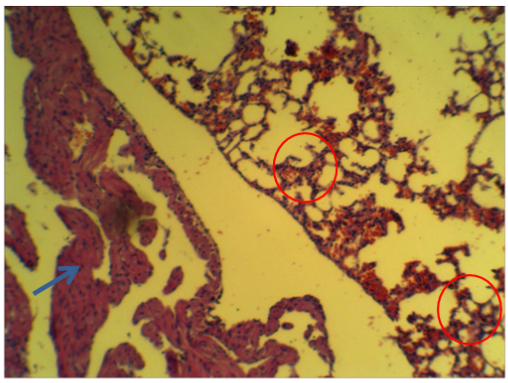
A Tumor

Figure 26: Blue arrow - skin. Red arrow - subcutaneous adipose tissue. Blue circle - necrotic tissue. Red circle - tumor cell proliferates. Black arrow - platysma striated muscle tissue.



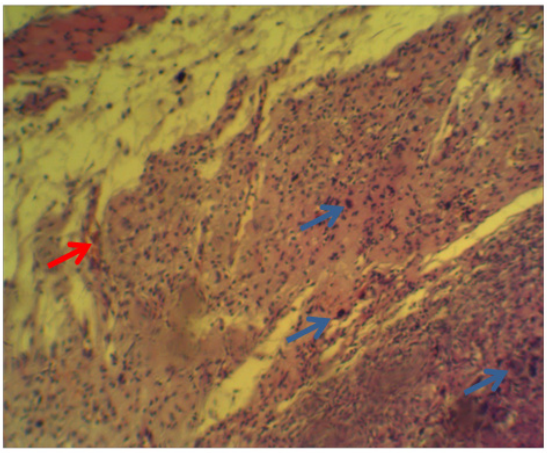
Liver

Figure 27: Tumor cells are not fixed. Blue arrow - hepatocytes around the blood vessel.



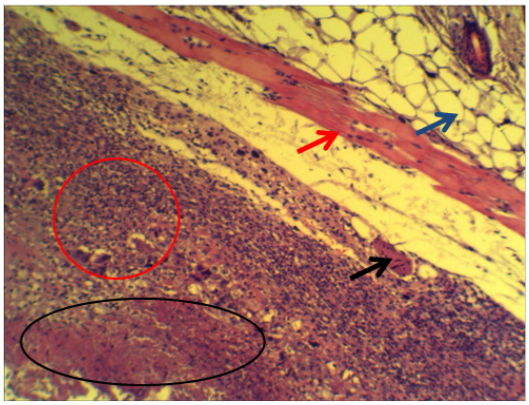
B. Lung

Figure 28: Red circle - pulmonary alveoli, exposed alveolocytes. Blue arrow - fibrous tissue. Here too, based on the results of morphological examination, no tumor metastases were seen in the liver and lungs.



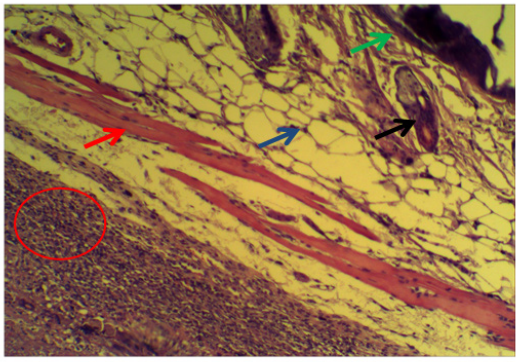
B. Tumor

Figure 29: Red arrow - blood vessel, erythrocytes. Blue arrow - tumor cells.



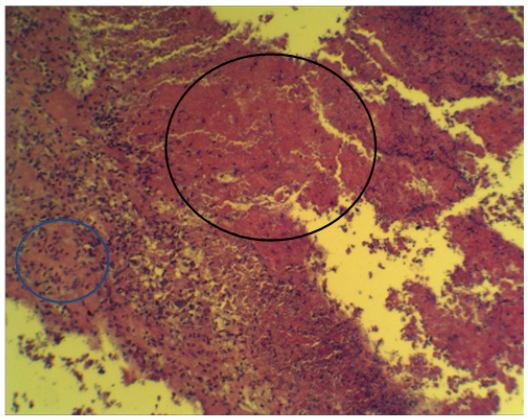
B. Tumor

Figure 30: Blue arrow - subcutaneous adipose tissue. Red arrow - platysma striated muscle tissue. Black arrow - nerve fiber. Red circle - tumor cell proliferation. Black oval - necrosis focus.



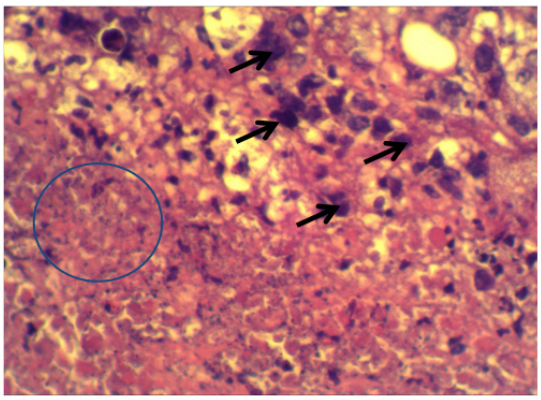
B. Tumor

Figure 31: Blue arrow - subcutaneous adipose tissue. Red arrow - platysma striated muscle tissue. Black arrow - hair bulb. Green arrow - skin, epidermis. Red circle - tumor cell proliferation



B. Tumor

Figure 32: Black circle - necrosis center. Blue circle - proliferates of surviving tumor cells.



B. Tumor

Figure 33: Black arrow - tumor cell, hyperchromic and sharply polymorphic nucleiiT. Blue circle - focal necrosis.

The antitumor effect is assessed by reducing the tumor mass, necrosis of tumor tissue, and complete disappearance of the tumor. Also, the tumor tissue was studied in dynamics by the method of morphological research, tumor necrosis, and correlation of tumor mass and necrotic areas. Based on the results of the morphological research, it was determined that the liver and lungs (the main target organs) are intact, and secondary tumor lesions are not recorded. After three sessions of hyperthermic treatment, a decrease in the size of the tumor formation and necrosis of the disease are visually observed in animals of all groups. And massive necrosis, after seven sessions. In all cases, necrosis and ulceration of the disease are observed, which indicates the transition to the phase of tumor healing.

After eight to ten sessions, necrosis and ulceration of the disease are again observed, which indicates the irreversibility of the process and the effectiveness of the hyperthermic method used. In all cases, the inhibition of tumor growth and intratumoral necrosis are due to the effects of hyperthermia. The results of visual observations are confirmed in all animals: measurements and photographs taken after three, seven, and ten sessions.

We have developed an innovative technology for patients called "*Cancerthermia*". Below, we will focus on the aspect of innovation of the technology. A wrung piece of thin fabric that was dipped in 42-45^{0}C water is applied on the tumor area identified during the preliminary examinations. On the peace of fabric, 25x18 cm (or any other size) 45^{0}C thermopad of our instrumentis placed until the fabric runs dry (time is empirical), in order to ensure the *precursor pre-treatment* of the patient's skin, to open and expand the pores, so that the heat emitted from the thermopad penetrates deeper into the diseased area to make cancer cells to be more likely affected by "*Cancerthermia"* and killed. Thereafter, the temperature on the equipment should be lowered to 43^{0}C, and the session continued for a period of about 40-80 minutes, depending on how the patient and the disease itself responds to "*Cancerthermia"*. When using the above mentioned technology in the clinic, the results have been achieved after 7 – 8 sessions, instead of 10-12 sessions, which is beneficial to the patients both psychologically and financially. Innovative method and anti blastoma technology results proved to have a success at "Integra" Oncology Clinical Center in Kutaisi, where our medical equipment to treat cancer using a controlled local "*Cancerthermia"* method was introduced in the first stage of treatment by this method, the clinic achieved good results in all cancer patients (Figures 35-41). Patient treatment is ongoing and the results are equally positive. The anticancer effect is evaluated by reduction of tumor mass, necrosis, and outright disappearance of the tumor. In addition, tumor tissue dynamics has been studied using morphological method, by correlation between tumor necrosis and tumor mass and necrotic areas. This technological innovative method, which we named as "Cancerthermia".

The morphological study showed that liver and lungs (primary target organs) are intact, secondary tumor lesions are not observed. No metastatic lesions were observed in the organs.

Therefore, based on the available material we can say that there is no metastasis in these organs during tumor mass lysis as a result of Local controlled "Cancerthermia".

Figure 34: Clinical therapeutic apparatus "LEZI-I" for local controlled cancerthermia, created at the Bionanoceramic and Nanocomposites Material Science Center of Georgian Technical UNiversity (head: Professor Z.Kovziridze). Certificate 6193. 18.02.2015. Georgian Patent).

This apparatus can be used for treating any body, less brain, rectum and cervix uterus. We offer MRT images of bodies of some cancer patients as a characteristic example, which show clearly cancer formations up to therapy and their disappearance or decrease within three seances after treatment: ovaries, stomach and lung. Full cycle consists from 6-7 seances.

Clinical Case 1

- Patient : 55 years old.
- Ds: NSCLC
- stage 3

pT3N2M0

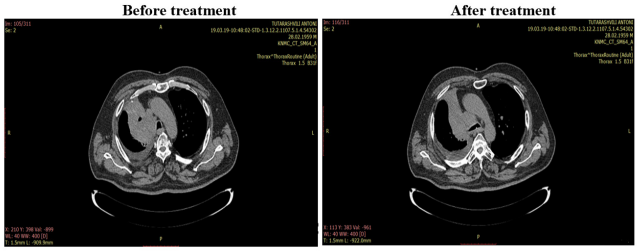


Figure 35:

Clinical Case 2

- Patient: I.L 28 years old
- DS: NSCLC
- Stage 4

pT2N2M1

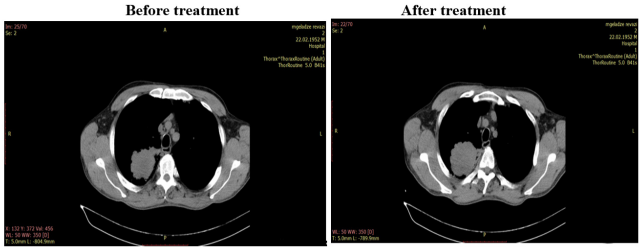


Figure 36:

Clinical Case 3

- Patient: V.CH.58 years old
- DS: NCSLC
- Stage:4

PT2N1M1

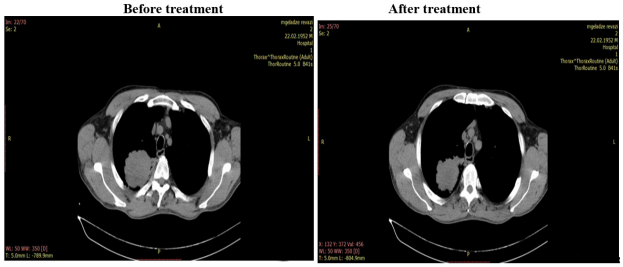


Figure 37:

Clinical Case 4

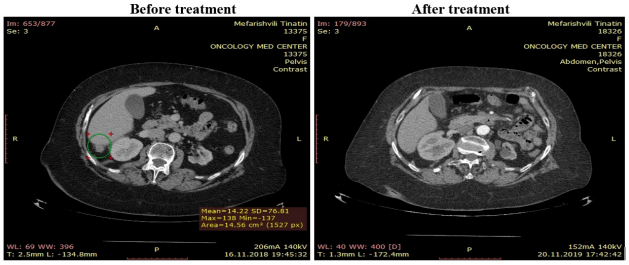


Figure 38: Patient with malignant ovaries cancer; C56 III stage, II cl. Group.

Clinical case 5

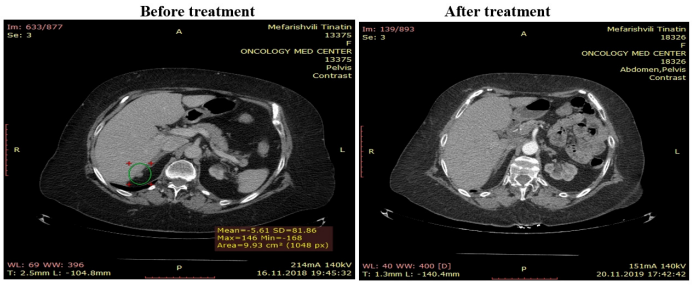


Figure 39:
Picture 15. Malignant gastric cancer C16.9 II stage, II cl. Group.

Clinical Case 6

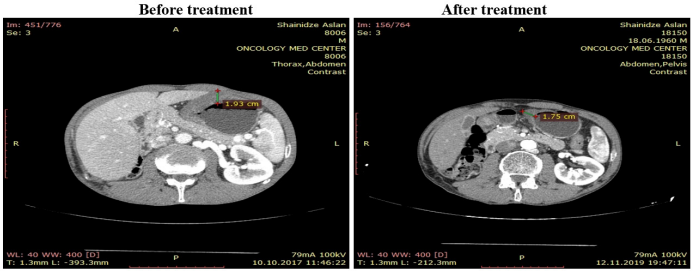


Figure 40:

Clinical case 7

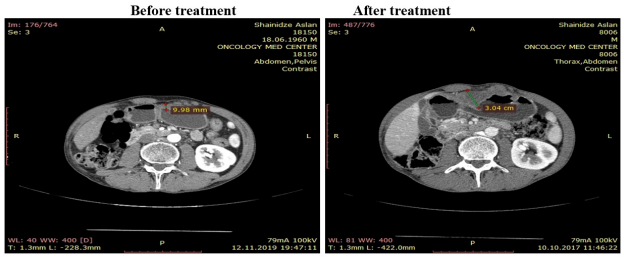


Figure 41:

Conclusion

The ultimate goal of the work: to create an innovative high-tech controlled local "cancerthermia" method created by us for the treatment of cancer tumors in the clinic for patients. innovative high-tech guided local “cancerthermia” has been developed as a monotherapeutic and adjuvant anti-tumor effect, using our devices “LEZI-1”, In polychemotherapy treatment of tumors.

Modern methods are used to conduct research: MRT, chemical, thermal, X-ray structural, electronic and biological microscopy, etc. Advantages of our work and the uniqueness lies in the fact that the controlled local "cancerthermia" treatment is harmless to human health and is not characterized by any side effects. and as a result has great advantages over surgical, chemo- and radiation therapy.

Based on the above, the importance of the research, both for Georgia and internationally, for both the social situation and technological development, is invaluable.

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