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Treatment of skin and subcutaneous cancer diseases by hyperthermic methods

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Original Article

Abstract

Purpose: The present work pursues perfection of highly efficient anticancer, principally new methodology and technology. It deals with the comparative study of anticancer activity of controlled local hyperthermia in animals and development of optimal regimes and schemes. Furthermore, it also presents the work on new clinical device of high anticancer effect. **Methods:** Authors used controlled local hyperthermia for this study. In our experiments, we used 3 to 3.5 months-old non-pedigree (nonlinear) white mice (mass: 18-30 gram). After mice selection for the experiments, animals were placed in vivarium, in quarantine regime for 10 to 4 days. Individual protocols were drawn for each animal. Similar feeding and handling regimes were created for all animals. Transplantable malignant cancer strain, Erlich adenocarcinoma, was used. **Results:** Experiments on animals were successful. There are positive conclusions of pathological-anatomy laboratory "PathGeo": Form # IV -200- 6A, for the examination 3119-12 and # 15/02 and macro-morphological and micro-morphological description of the study # 15272-13. On the basis of results of morphological study, it was proved that liver and lungs (the main target bodies) were intact, and secondary cancer injuries were not fixed. After three sessions of hyperthermia treatment, the decrease in sizes of cancer formations and necrosis diseased sections were visualized, while massive necrosis was observed after seven sessions. In all cases, necrosis and ulceration diseased places were observed, which refers to transition of cancer into phase of healing. After eight-ten sessions, necrosis of cancer and ulceration were observed, which refers to irreversibility of the process and efficiency of the applied method of hyperthermia. **Conclusion:** Anticancer effect of hyperthermia conditioned by temperature fields was proved, which was expressed in inhibition of cancer growth, resorption and increase of life length of experimental animals. The method of treatment was selected with maximum anticancer effect free of side effects and was offered as a new, perspective alternative or additional for treatment of malignant cancers.

Keywords: Controlled Local Hyperthermia; Necrosis; Ulceration; Metastasis.

Introduction

According to the data of the World Health Organization (WHO), morbidity and lethality index that is conditioned by melignancies has been growing permanently all over the world. Today, the leading role in treatment of oncology patients is attributed to surgical methods, chemo- and radiation therapy. Immuno- and hormone therapies are considered as addition to the main methods of treatment.[1-14]

Although in frequent cases, irrespective of skillfully performed surgeries, lethal outcomes have been reported. Alongside with poly-organic insufficiency, this is caused by suppression of immune system induced by chemo-radiotherapy, myelodepression, leucopenia, cardio, nefro-, hepato- and neuro-toxicity, inter-current microbial complications and others. These conditions necessitate the search of new approaches of treatment of malignancies focused on amplification of anti-cancer strategies.[15-24]

In this study, anti-cancer effect of hyperthermia has been investigated. Hyperthermia is a method, which implies citostatic impact on cancer cells by increase of temperature in cell - by the mechanisms of thermal dissipation conditioned by hyperthermic field. The working team consisted of ceramists, oncologists, physicists, immunologists, and specialists of electronics sphere. On the basis of experimental materials used in this study, the impact of anti-cancer mono--therapeutic treatment and its adventitial effect in poly-chemo-therapeutic treatment of cancers have been presented for the first time in Georgia. With this in view rational hyperthermia schemes were developed.[25-31]

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Authors have created a device called "Lezi". For the improvement of "Lezi's" efficiency, a clinical device "Lezi 1" was constructed in order to shift treatment to a clinic for treatment of patients at the starting stage after an agreement with the Oncology Center. It should be emphasized that experiments on animals were successful. There is a positive conclusion of laboratory of Morbid Anatomy "PathGeo", Form # IV-200 -6/A about macro-morphologic and micro-morphologic description.

The significance of the work is that by hyperthermic head/nose of a device created by us in laboratory conditions (**Figure 1**), temperature field is transported to animal skin and underneath it. The nose can be placed on the cancer site for a definite time, which was determined empirically, based on the reaction of an animal and disease to the treatment.

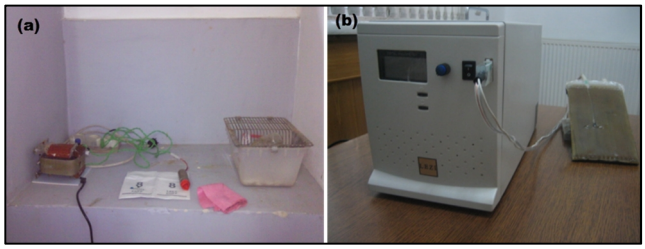

FIG. 1: (a) Laboratory device "Lezi" (left), cage with mice (right); (b) Clinical therapeutic device "Lezi 1" created at the Bionanoceramic and Nanocomposite Materials Science Center of Georgian Technical University.

In this research project, authors expect to provide:

1. Confirmation of anti-cancer effect of hyperthermia conditioned by temperature fields, to be expressed in inhibition of cancer growth, possible resorption, and increase of life length of experimental animal.
2. Selection of optimal anti-cancer method with minimal side effects (or without these effects) and its offering as a new, perspective alternative or additional therapeutic means against malignant tumors/cancers.

Methods and Materials

Hyperthermia is a Greek word and it means warming and overheating. It is one of the declared methods for cancer therapy in USA, Europe, and Japan with no contra-indications. Two forms of hyperthermia are used against oncology diseases: hyperthermia of the whole body and/or local hyperthermia. In this case, internal temperature of the whole body or any concrete body is increased from 42°C to 44°C, resulting in destruction of tumor cells. This does not mean simple warming of external part of a body; it implies heating of the whole body or only cancer formation sections, by means of micro- or radio- waves, as well as by exposure to infrared (IR) radiation.

In our experiments, we used 3 to 3.5 months-old non-pedigree (non-linear) white mice (18-30 g mass). After their selection for experiments, within 10-14 days animals were placed in vivarium, in quarantine regime. Individual protocols were drawn for each separate animal. Animals were kept at similar nutrition and handling conditions. Experiments were carried out by the use of Erlich adenocarcinoma (EAT, ascitic version) and S-45 (sarcoma fusocellulare) cancer strains. Inoculation of Erlich adenocarcinoma was performed (by oncologists) in mice, intra-peritoneally, that of S-45- subcutaneously, in subscapular zone. Injection of the studied preparation was made peri- and intra-tumorally.

Experiments were performed by the methods widely used in experimental oncology. Anti-cancer effect of the studied preparation was considered according to frequency of cancer formation, growth inhibition, animal weight change, ascitic liquid reduction, and changes in indices of animal life prolongation.

Mono-therapeutic anti-cancer effect of hyperthermia

We have been studying anti-cancer effect of hyperthermia since 2007. On the first day of the experiment (June 06, 2013), subcutaneous inoculation of EAT cancer strain was performed in the vivarium of State Medical University in Tbilisi, Georgia. All animals of experimental group developed cancer. Animals were shifted from the vivarium of the State Medical University to the vivarium of Bionanoceramic and Nanocomposite Science Center of Georgian Technical University for the commencement of their treatment.

On July 04, 2013, we measured animal cancers (see **Table 2**), and on the very day we carried out the first session of hyperthermia. Nose of the hyperthermia device, on the top of which temperature reached 42°C to 44°C, was placed on cancer formation. Length of hyperthermia manipulation equaled to 30 minutes.

Experiments proved that in #1, 2, and 3 animals cancer growth was inhibited (suspended). Necrosis was already detected by the fourth session. In the fourth session, as a result of treatment by hyperthermia, we observed the so-called "intra tumor necrosis", that is, necrosis of cancer cells was developed. During treatment of skin and subcutaneous cancers/tumors by the methods of hyperthermia (first group) experiments were carried out on 12 groups, but we are offering here the results of the last two groups, as common characteristic ones. After every two or three sessions cancers of animals were photographed. Pictures are given in **Figures 2-6**.

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TABLE 1: Results of experiments on animals

	# 1 animal cancer sizes L, B, H= 12 × 10 × 8 mm	# 2 animal cancer sizes L, B, H= 12 × 10 × 8 mm	# 3 animal cancer sizes L, B, H= 14 × 14 × 10 mm
Length of the I session) (July 04, 2013)	30 min (Inhibition of cancer growth is observed)	30 min (Inhibition of cancer growth is observed)	30 min (Inhibition of cancer growth is observed)
Length of the II session (July 06, 2013)	30 min	30 min	30 min
Length of the III session (July 08, 2013)	30 min (Necrosis is observed)	30 min (Necrosis is observed)	30 min (Necrosis is observed)
Length of the IV session (July 10, 2013)	30 min (Necrosis is observed; cancer sizes 12 × 12 × 8 mm)	30 min (Ulceration around diseased site is observed; cancer sizes 10 × 8 × 5 mm)	35 min (Necrosis is observed; cancer sizes 10 × 8 × 8 mm)
Length of the V session (July 12, 2013)	35 min (Ulceration is observed; around necrotic zone)	35 min (Ulceration is observed; around necrotic zone)	35 min (Ulceration is observed; around necrotic zone)
Length of the VI session (July 14, 2013)	35 min	35 min	25 min
Length of the VII session (July 16, 2013)	35 min	35 min	(Was not subjected because of acute ulceration)
Length of VIII session) (July 18, 2013)	30 min (Ulceration around cancer zone, there is no cancer; sizes of treated section 12 × 12 × 3 mm)	30 min (Ulceration around cancer zone, there is no cancer; sizes of treated section 8 × 5 × 3 mm)	30 min (Ulceration around cancer zone, there is no cancer; sizes of treated section 3 × 3 × 3 mm)

Abbreviations: L = length; B = breadth; H = height

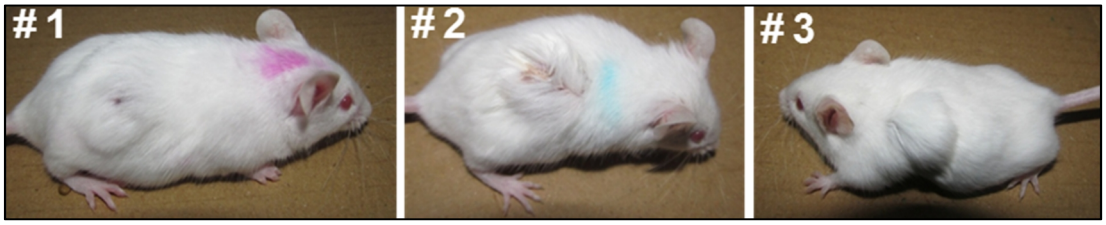

FIG. 2: After the first session (July 04, 2013) [#1 has two cancer formations]

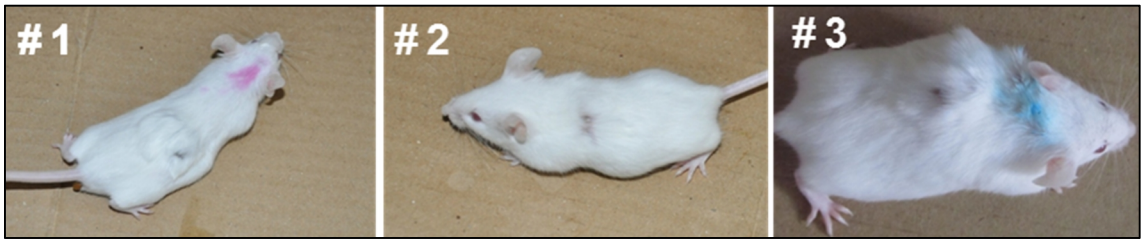

FIG. 3: After the third session (July 08, 2013) [#1-has two cancer formations]

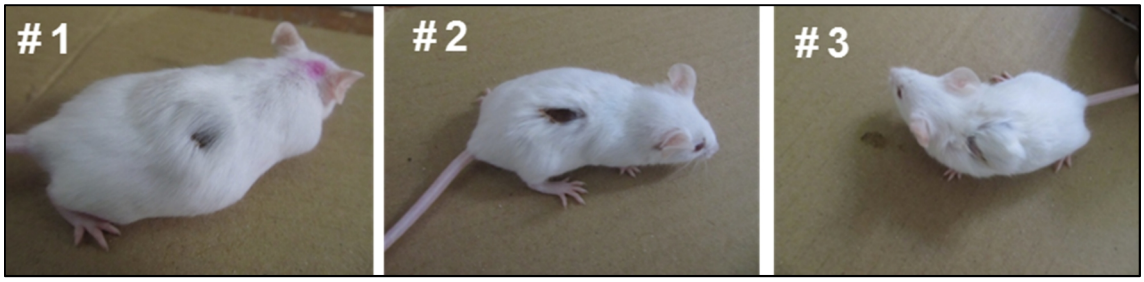

FIG. 4: After the fifth session (July 12, 2013) [#1 has two cancer formations]

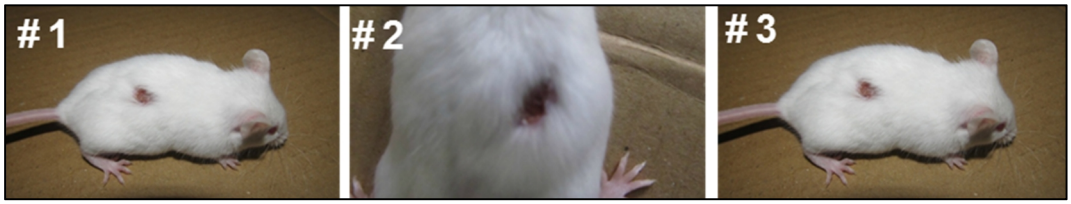

FIG. 5: After the eighth session (July 18, 2013) [#1 has two cancer formations]

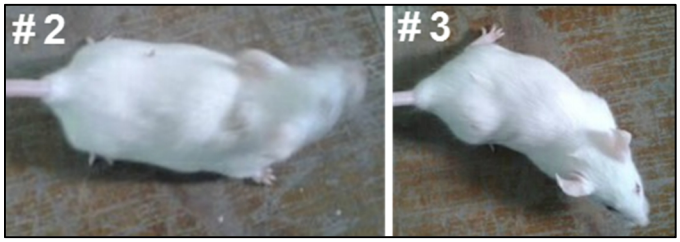

FIG. 6: Treated animals by the end of December 2013 (six months after termination of treatment).

Results and Discussion

After the very first session of the experiment, suspension of tumor growth was observed in all three animals of the first group, while after the third session, all three animals revealed necrosis of cancer cells. Necrosis that was developed in #2 animal of the first group considered in the paper was apparent at the fourth session. The #2 animal revealed ulceration around the diseased section after the fourth session. In the process of experiments mice positively responded to the process of therapy.

After the fifth session, all three animals of the first group, which were considered in the paper, revealed ulceration around diseased section. We received #1 animal with two cancer formations. One was treated and the other was left without treatment just for comparison. In the process of therapy, necrosis of the treated cancer was clearly detectable, while the other tumor continued to grow. After the eighth session, complete necrosis of the treated cancer formation and ulceration around cancer sections were observed, which refers to transition of a disease to the phase of healing. The #1 animal, which had a tumor that was left untreated, died in three weeks after the end of treatment. Almost the same results are presented for animals of the second group. Animals were under permanent post-treatment observation. Six months after the completion of the treatment cancer was cured.

Anticancer effect, in the case of the first group and the secgroup, was assessed according to the decrease of cancer mass, cancer tissue necrosis, and complete disappearance of cancer. Likewise, cancer tissue was studied in dynamics by morphological method, by correlation of cancer necrosis and cancer mass and necrotic sections. On the basis of the results of morphological study, it was proved that liver and lungs (the main target bodies) were intact, and secondary cancer were not fixed.After three sessions of hyperthermia treatment, in both groups given in the paper, decrease in sizes of cancer formations and necrosis of diseased sections were visualized, while massive necrosis was observed after seven sessions. In all cases, necrosis and ulceration of diseased were observed, which refers to transition of cancer into of healing. After eight-ten sessions, again necrosis of cancer and ulceration were observed, which refers to irreversibility of the process and efficiency of the applied method of hyperthermia.

This phenomenon was characteristic for mice of twelve groups, which were subjected to controlled local hyperthermia within these years. In all, experiments were performed on 55 to 60 mice, and inhibition of cancer growth and intra-tumor necrosis were conditioned by the effect of controlled local hyperthermia used by us. Visual observations were confirmed by the results obtained for all animals: by measurements and photos made after three, seven, and ten sessions.

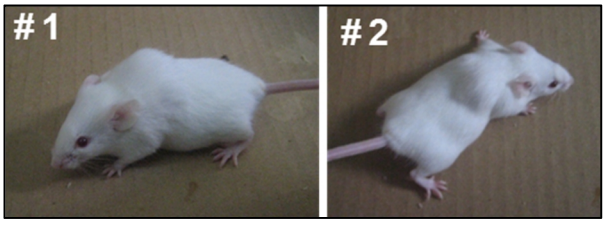

FIG. 7: After the first session (December 10, 2013)

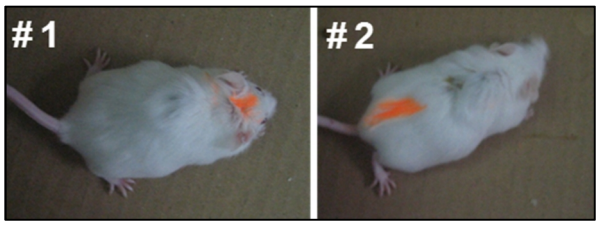

FIG. 8: After the third session (December 14, 2013)

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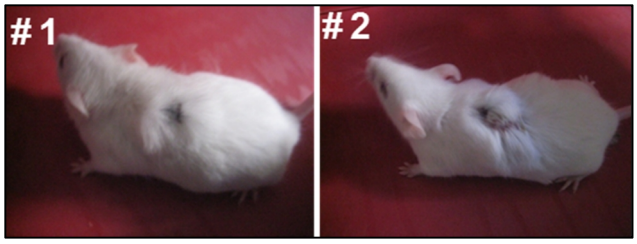

FIG. 9: After the sixth session (December 22, 2013)

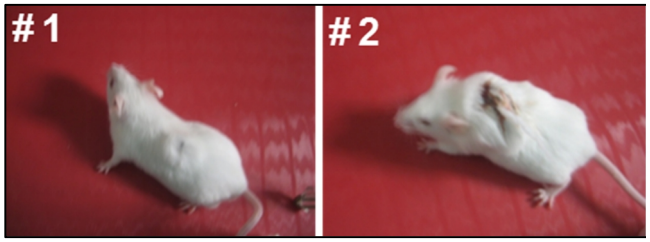

FIG. 10: After the eighth session (December 26, 2013)

TABLE 2: Treatment of skin and subcutaneous cancer diseases by hyper thermal methods (second demonstration group)

	Animal	
	#1	#2
Sizes before treatment (December 10, 2013)	8 × 6 × 5 mm	10 × 7 × 5 mm
Duration of the I session (December 10, 2013)	25 min	25 min
Duration of the II session (December 12, 2013)	30 min	30 min
Duration of the III session (December 14, 2013)	30 min	30 min
Sizes after the IV session (December 16, 2013)	9 × 7 × 5 mm	14 × 11 × 8 mm
Duration of the IV session (December 16, 2013)	30 min	30 min
Duration of the V session (December 18, 2013)	30 min	30 min
Duration of the VI session (December 20, 2013)	35 min	35 min
Sizes after the VI session (December 22, 2013) Necrosis is observed	7 × 6 × 5 mm	16 × 14 × 9 mm
Duration of the VII session (December 22, 2013)	30 min	
Duration of the VIII session (December 24, 2013)	30 min	
Duration of the IX session (December 26, 2013)	30 min	
Note:	After the VII session, we stopped sessions with #2 mouse, because lymph started leaking from cancer. It was subjected to higher than needed temperature: 44-46^0 C	

Three or four sessions were left to the end of treatment, but on the advice of oncologists both animals were butchered, and liver and lung analyses were performed at the Laboratory of Morbid-Anatomy "PathGeo", to see the possibility of metastasis spreading in those bodies. Analysis with corresponding figures and descriptions are provided below.

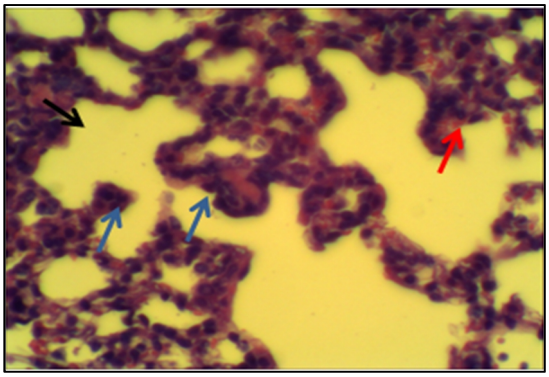

FIG. 11: Liver, animal #1; Black arrow shows blood tube, with the presence of erythrocytes in it; Blue arrow shows hepatocytes around blood tube (liver cell); [Cancer cells are not fixed in preparation]

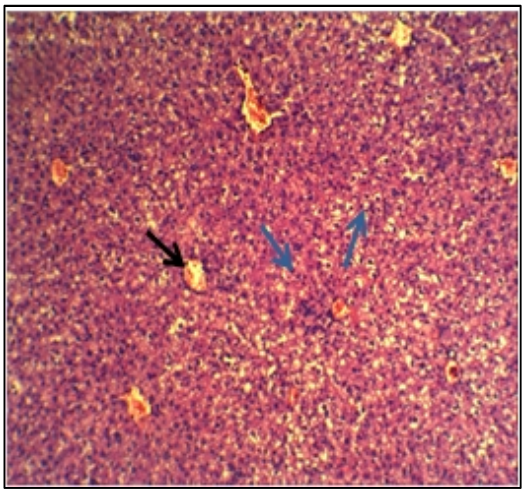

FIG. 12: Liver, animal #1; Black arrow shows lung alveolus; Blue arrow shows the first order alveolocytes; Red arrow shows erythrocyte; [Cancer cells are not observed in this preparation. On the basis of results of morphological study no cancer cells were found in liver and lungs]

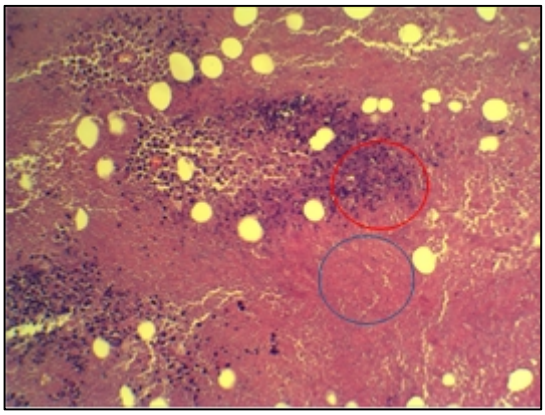

FIG. 13: Cancer, animal #1; Blue circle shows necrotic masses; Red circle shows cariorexis (process of cell nucleus degradation); [Cancer cells are fixed, with acute polymorphism which is inherent to Erlich adenocarcinoma]

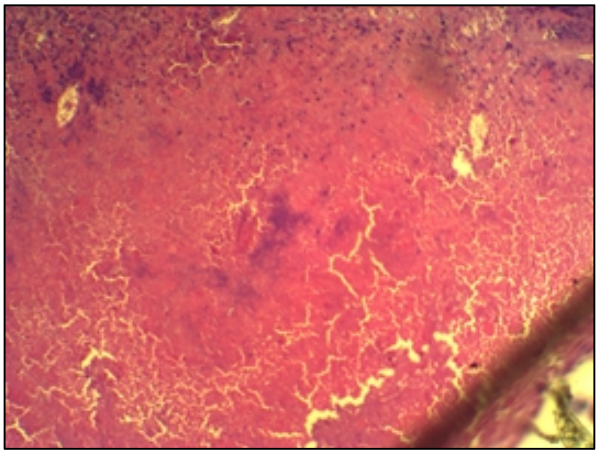

FIG. 14: Cancer, animal #1; [This figure shows necrosis]

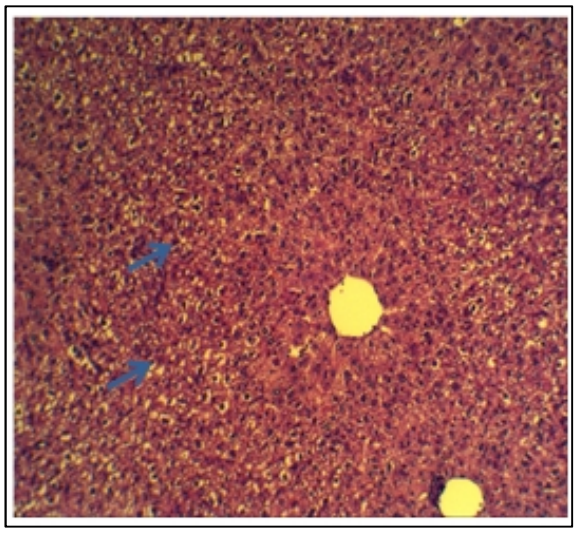

FIG. 15: Liver, animal #2; Blue arrow refers to hepatocytes around blood tube; [Cancer cells are not fixed]

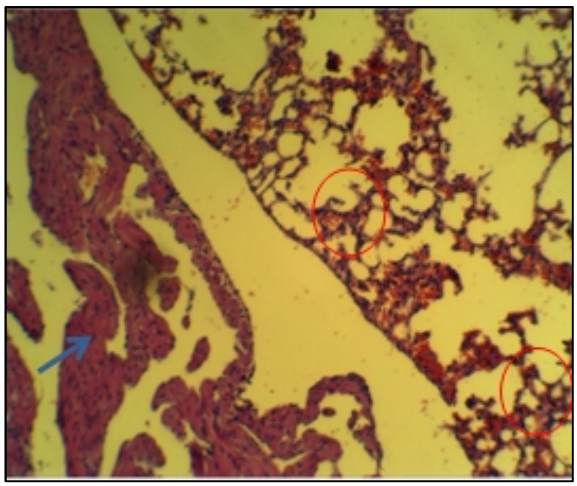

FIG. 16: Liver, animal #2; Red circle shows lung alveoli, bedded with alveolocytes; Blue arrow shows fibrotic tissue; [according to the results of morphological studies, there are no cancer metastasis in liver and lung]

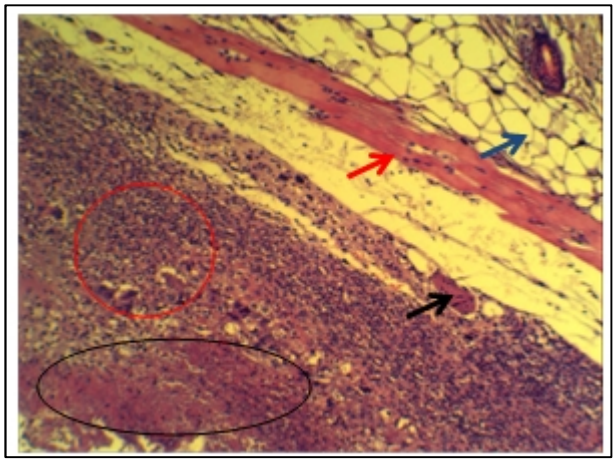

FIG. 17: Cancer, animal #2; Blue arrow shows subcutaneous fatty tissue; Red arrow shows longitudinal muscle tissue of platisma; Black arrow shows nerve fiber; Red circle shows cancer cells proliferate; Black oval shows necrosis center

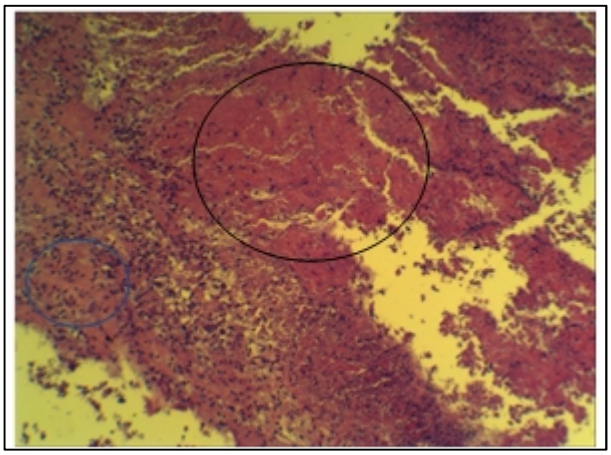

FIG. 18: Cancer, animal #2; Black circle shows necrosis center; Blue circle shows proliferates of traces of cancer cells

Conclusion

After measuring temperature by thermometer, it was proved that in tissues surrounding cancer temperature decreases and reached that of a body. The highest temperature was fixed in cancer projection area on skin and it equalled to 44°C. Within 10-12 mm distance from cancer tissue, we fixed normal body temperature. Anti-cancer effect was assessed by decrease of cancer mass, necrosis of cancer tissue, and absolute disappearance of tumour. We have also studied the effect in dynamics by morphological study method of cancer tissue, cancer necrosis as well as correlation of cancer mass and necrotic sections. On the basis of results of morphological studies, it was proved that liver and lungs (the main target bodies) are intact, and secondary cancer damages are not fixed.

Furthermore, after three sessions of hyperthermia treatment, the decrease in sizes of cancer formations and necrosis of diseased sites were observed in all animals, whereas massive

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necrosis was observed after seven sessions. In all cases, necrosis and ulceration were observed, which refers to irreversibility of the process and efficiency of the applied method of hyperthermia. Results of histo-pathologic studies proved vividly expressed anti-cancer effect of local hyperthermia. Figures offer cancer cells of polymorphous nucleus and vast zones of necrosis - which is the result of impact of high temperature on cancer tissue. It should be noted that 70-90% of cancer mass is necrotic, and central necrosis was observed. Metastatic injuries were not fixed in the bodies. On the basis of the available material, we can state that at lysis of cancer mass that is conditioned by local hyperthermia, and the formation of metastasis does not develop in the studied bodies.

Finally, our group has constructed a new clinical device "Lezi 1" (**Figure 1 (b)**), which will be utilized at the Clinical Oncology Institute, in Tbilisi. Five volunteers (patients) will be subjected to treatment of surface cancer diseases by the method of hyperthermia developed by our research group. In the near future, we plan to create a new device for treatment of proctologic cancer diseases.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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