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Controlled Local Hyperthermia Device for Treatment of Proctologic (Rectal) and Cervical Cancer : Safety Evaluation in White Rats

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Abstract

Objective: *Investigation of the mono-therapeutic effect of hyperthermia against proctological and cervical cancer.*

Method: *For the development of the controlled local hyperthermia method, the experimental device "LEZI," created at the Center for Bio-Nanoceramics and Nanocomposite Materials Science, Georgian Technical University, was employed. Studies were conducted on experimental animals. Results: In all experimental animals (three-month-old albino rats), tumor growth was arrested, and intratumoral necrosis developed. This method is registered with the National Intellectual Property Center of Georgia (Sakpatenti), Certificate of Deposit No. 5054: "Controlled Local Hyperthermia and Magnetic Hyperthermia for Cancer Treatment."*

Conclusion: *As a result, it was demonstrated and confirmed that after 7–10 treatment sessions, the tumor ulcerated, indicating positive experimental outcomes (Pathological-Anatomical Laboratory "PathGeo," Investigation #3119-12, Histopathological Examination #15272-13, diagnosis issued on 14.01.2014, Tbilisi, Georgia).*

Safety: *The experiment confirmed that the method is safe for animals during treatment.*

Keywords: controlled local hyperthermia, necrosis, ulceration, metastasis, experiment, safety, therapy.

Introduction

Relevance of the Problem and Novelty of the Research

According to the World Health Organization, both the incidence and mortality rates of malignant tumors are steadily increasing worldwide. At present, the treatment of oncological patients is primarily based on the following modalities:

1. Surgical interventions;
2. Chemotherapy;
3. Radiation therapy.

Hormone therapy and immunotherapy serve as adjunct treatment modalities. However, in many cases, despite appropriately and professionally performed interventions, the disease ultimately results in a fatal outcome. In addition to multiple organ failure, this is attributable to chemotherapy- and radiotherapy-induced suppression of the immune system, myelodepression, leukopenia, cardio-, nephro-, hepato- and neurotoxicity, as well as intercurrent microbial complications, among other factors. Collectively, these circumstances necessitate the search for new approaches to the treatment of malignant neoplasms aimed at strengthening antitumor therapeutic strategies.

For the first time in Georgia, the antitumor effects of controlled local hyperthermia are being investigated. Hyperthermia is a therapeutic approach that exerts cytostatic effects on cancer cells by elevating intracellular temperature, which in this study is achieved through thermal diffusion induced by a controlled temperature field.

Approximately 7.000 – 10. 000 new cancer cases are diagnosed annually in Georgia, with total prevalence reaching 90.000.

It is well known that malignant tumors consist of the body's own cells, which differ from normal cells primarily by their uncontrolled and unlimited proliferation and growth. Consequently, the intensity of metabolic processes and, accordingly, the energy requirements in malignant tumors are higher than in normal tissues. Therefore, it is promising to apply interventions to affected tissues and their surrounding areas that, within a defined time interval, depletes the energy potential of the transformed cells, induces protein denaturation (cell death), while simultaneously preserving the viability of healthy cells [1–9].

Such a biophysical effect can be induced by local hyperthermia (+42 to +44 °C).

The incidence and mortality of malignant tumors are steadily increasing worldwide, showing no signs of decline. Early diagnosis remains challenging, and a significant proportion of patients are admitted with advanced-stage tumors (stage III–IV), requiring complex multimodal treatment, including surgery, radiotherapy, and chemotherapy. The number of patients presenting to oncologists with late clinical signs and associated metabolic disorders has also risen.

Developing new methods for treating malignant tumors remains a critical task in oncology. The introduction of a drug or treatment modality into clinical practice, supported by positive results from experimental and clinical studies, represents a significant advancement in the field.

Main Part

Objectives of the Hyperthermia Research

The aim of this study is to improve both short- and long-term treatment outcomes in oncological patients through the application of controlled local hyperthermia to malignant tumors.

Specific Objectives

1. To investigate the antitumor therapeutic effect of hyperthermia in experimental tumors.
2. To evaluate the adjuvant potential of hyperthermia in combination with polychemotherapy.
3. To study different hyperthermia regimens and their impact on immediate and long-term therapeutic results.

Scientific Novelty

For the first time in Georgia, an experimental study was conducted on the antitumor effects of controlled local hyperthermia, both as a monotherapy and as an adjuvant to polychemotherapy. The study demonstrated its efficacy in improving the short- and long-term outcomes of oncological treatment for patients with malignant tumors.

Research Object and Aim

The object of this study comprised 2–3-month-old, 20–25 g mass, outbred white rats and their malignant tumor cells. Cancer cells typically die at approximately 42–44 °C due to insufficient oxygen supply through blood vessels, whereas normal cells remain unharmed even at higher temperatures. Furthermore, tumors are more easily heated than the surrounding normal tissue because their vascular and nervous networks are less developed, and their oxygen supply is lower compared to healthy cells [1–15].

The experiment was conducted on twelve groups of animals, and positive results were consistently observed across all groups. These findings have been published in Japan, the USA, Europe, and Georgia, and presented at international conferences and world congresses [16–20].

Based on these results and several years of accumulated experience, motivation arose to develop clinical equipment for volunteer patients. This device, designed for the treatment of oncological diseases of the rectum and cervix using controlled local hyperthermia, was created at the Center for Bionanoceramics and Nanocomposite Materials at the Georgian Technical University.

Aim of the Work

The aim of this work is to develop a clinical device for the treatment of proctological (rectal) and cervical diseases and to test it in animals to achieve controlled local hyperthermia. The device enables the targeted delivery of a temperature field within living tissue for the treatment of rectal and cervical malignant tumors.

Principle of Operation

The essence of the work lies in the transport of a controlled temperature field to the tumor site using a hydro-hyperthermic method. In a human volunteer patient, this is achieved through the probe (hyperthermic head) of the clinical device developed by us (Fig. 1). The hyperthermic head is inserted directly into the tumor area for a predefined period, which is determined empirically based on the patient's individual response to therapy and the sensitivity of the disease to treatment. According to these parameters, the therapeutic temperature range is maintained at 42–44 °C, with an exposure duration of 30 – 60 minutes.

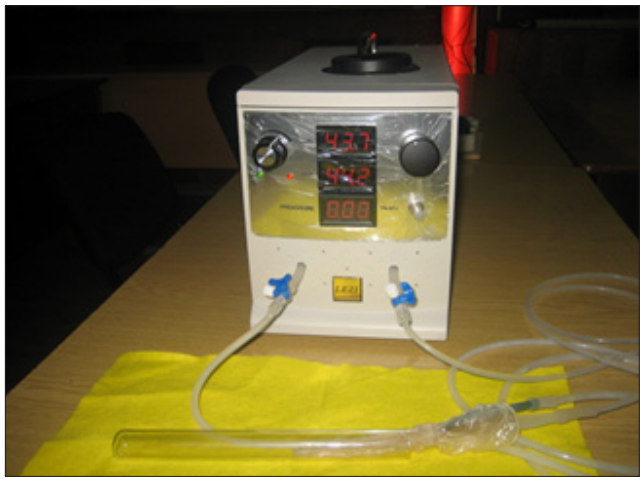

Figure 1: Clinical device for the treatment of proctological (rectal) and cervical oncological diseases using the method of controlled local hyperthermia. The device was developed at the Center for Bionanoceramics and Nanocomposite Materials Science, Georgian Technical University (Head: Prof. Z. Kovziridze).

Technical Specifications

- Power supply: 220 V, 160 W
- Heater power supply: 60 V, 100 W
- Tank volume: 0.5 L
- Outlet temperature adjustment range: 40.5–47.0 °C
- Fluid flow rate through the probe: 250 mL/min

The device is constructed using medical-grade silicone drainage tubes, distributors, and other certified medical accessories. Temperature control is ensured by a three-sensor monitoring system. Two thermosensors are employed to measure the temperature of the circulating fluid at the inlet and outlet of the hydraulic circuit, with the corresponding values displayed on the control panel via a three-line digital display. A third temperature sensor is mounted directly on the heater and provides feedback to the electronic control circuit, enabling stable and reliable regulation of the thermal regime.

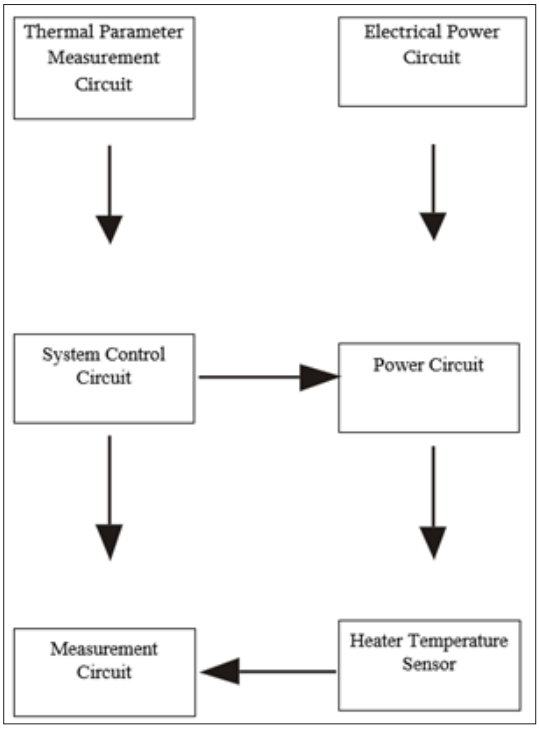

Figure 2: Schematic diagram of the electronic circuit for temperature stabilization.

Heating Unit

The heater consists of a high-purity silver tube (4 × 7 × 220 mm). Its active area is coated with a thermally conductive electrical insulation layer, over which a heating spiral is wound. A temperature sensor is mounted at the tube's outlet to monitor the temperature of the fluid flow. To minimize heat loss, the heater is fully enclosed in a thermally insulating protective shell.

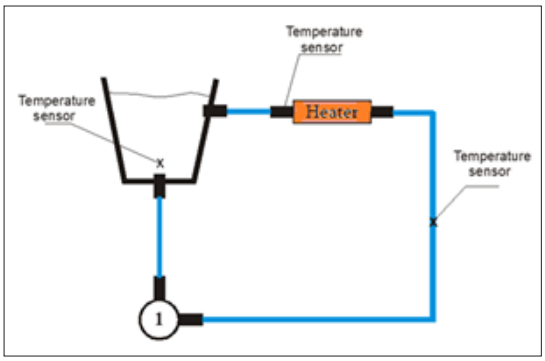

Figure 3: Functional diagram of the hydraulic system.

The hydraulic system is powered by three low-voltage, constant-current electric pumps. The electronic control unit for the pumps provides one standby mode and three operational modes (Table 1).

Table 1: The hydraulic system Operation Modes

Pump(s)	Operation Mode	Function / Purpose
PUMP1	Circulation through heater	Prepares the device; stabilizes tank fluid temperature via control panel (Fig. 3)
PUMP2 (reverse) + PUMP3	Air/fluid removal from probe	Facilitates insertion and removal of the sheathed probe
PUMP2 + PUMP3	Circulation within probe	Maintains fluid flow in the probe; fluid returns to the tank for reheating (Fig. 4)

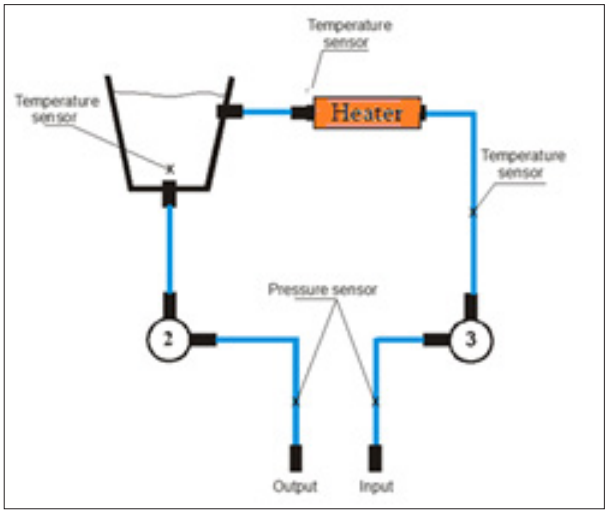

Figure 4: Functional diagram of the hydraulic system in treatment mode.

The hydraulic system control scheme ensures pump operation according to the mode selected from the control panel and regulates pump intensity to generate the required probe pressure (maximum 50 kPa). Excessive pressure may damage body tissues; the pressure can be adjusted within ±10% via the control panel. To achieve efficient heat transfer at the probe–tissue interface, the fluid flow is maintained at an appropriate speed. The electronic control system allows, based on clinical trial results, adjustment of fixed parameters over a wide range.

Inlet and outlet flow at the hydraulic system outlet are connected to the corresponding probe tubes using adapter-locks. Thick-walled silicone drainage tubes (2 × 5 mm for inlet, 3 × 6 mm for outlet) are used, with 4 × 8 mm silicone tubing for internal hydraulic connections. The thermal insulation properties of the thick-walled silicone minimize the influence of ambient temperature on the circulating fluid, ensuring stable temperature regulation over a wide range.

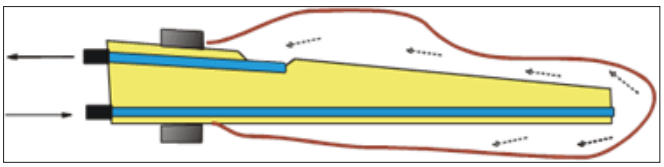

Figure 5: Probe for the treatment of rectal and cervical cancer using the hyperthermic method.

Probe (Hyperthermic Applicator)

The probe consists of a silicone tube covered by a thin-walled sheath (Fig. 5). The sheath prevents direct contact between circulating fluid and tissue, ensuring efficient heat transfer to adjacent organs.

Safety Assessment of Controlled Local Hyperthermia in White Rats

The aim was to evaluate safety using a shortened protocol.

Experimental Design

The method produces a stable local thermal field of 42–44 °C in subcutaneous tissues. White rats (20 ± 5 g) were divided into experimental and control groups (10 males and 10 females per group). A hyperthermic probe was inserted into the cervix and rectum of experimental animals. Each session lasted 3 minutes, repeated daily for 10 days, totaling 100 times the standard therapeutic exposure used in clinical practice (equivalent to 30 minutes). All animals underwent necropsy immediately after the last session to examine internal organs for any adverse effects.

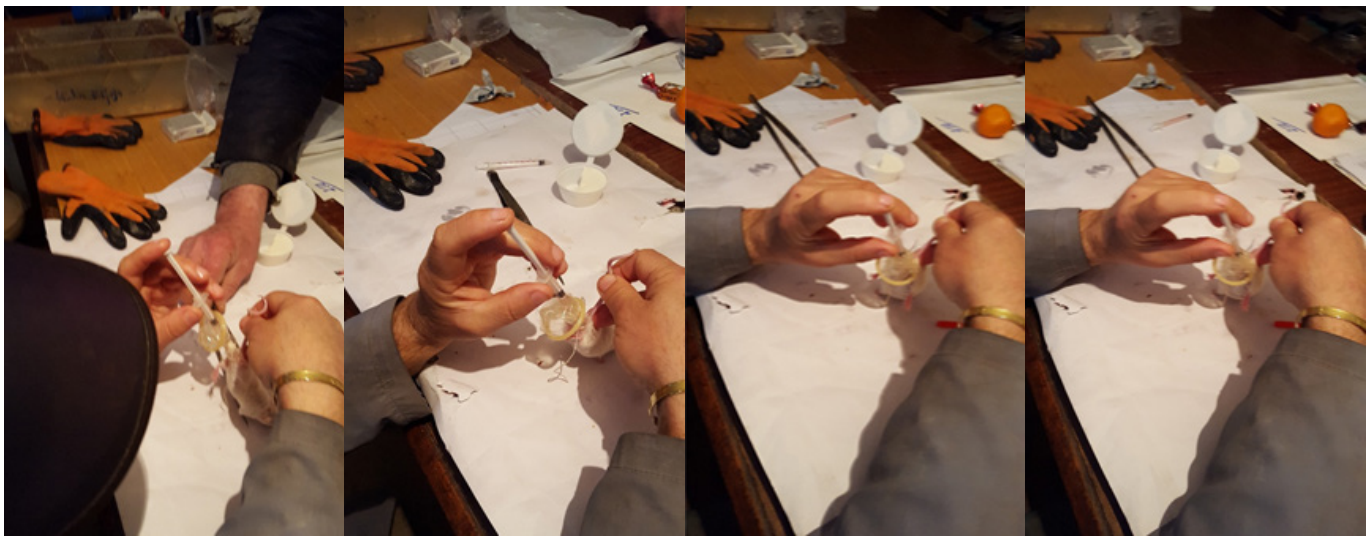

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Figure 6: Experimental setup for studying the safety of guided local hyperthermia in the cervix and rectum of test animals.

The aim of the study was to determine the lethal dose (LD_{50}) and to record any individual adverse effects observed in the animals.

Evaluation Criteria

The study was conducted using the Irwin scale to evaluate the effects of the treatment.

- Mood and emotionality: increased restlessness, aggressiveness
- Motor activity and CNS arousal: swaying, tail-wagging, trembling, convulsions
- Posture: prostration, stiffness, limb position (flexed or extended)
- Motor coordination: staggering, abnormal gait, standing reflex
- Muscle tone: grip strength, arched back, abdominal tension
- Reflexes: corneal reflex, ipsilateral flexion reflex
- Autonomic responses: pupil and eyelid changes, exophthalmos, urination, salivation, lacrimation, drooling, skin color changes
- Cardiorespiratory parameters: heart rate, respiratory rate
- Other outcomes: cyanosis or hyperemia, immediate or delayed death

Body weight was recorded at the start of the experiment and subsequently every 5 days.

Results

Observations were conducted for 10 minutes, and at 1, 2, and 4 hours after the procedure, followed by daily monitoring for 14 days. Throughout the experiment, no deviations from normal parameters were observed. All animals remained healthy and active, with normal orientation, olfactory responses, and motor skills. Restlessness and aggressiveness were absent, and posture, motor activity, muscle tone, and reflexes to external stimuli (noise, light, touch, pain) remained normal. Autonomic functions, including respiratory and heart rates, were within baseline ranges, and no visible abnormalities were noted.

Body weight gain, as well as food and water intake, were comparable to the control group. No falls or injuries occurred during the 14-day observation period. The absence of mortality precluded calculation of LD_{50}. It was concluded that a 100-fold increase in the duration of the procedure in rats did not produce lethal or adverse effects.

Macroscopic Examination

The rats' fur was clean and well-groomed, with pink, healthy skin on the limbs and ears. No areas of hair loss or discharge from natural openings were observed. Internal organs were in their normal anatomical positions. Tissues were clean, with moderately developed adipose tissue. The serous membranes appeared dewy, shiny, and transparent. The myocardium was firm, ventricular cavities were empty, and the endocardium was clean.

The lungs were pink, well-aerated (did not sink in water), with no parenchymal bruising or fluid accumulation. The liver and spleen were normal in size, with smooth, shiny surfaces and no visible lesions. Kidney capsules were easily removed; cortical and medullary structures were clearly distinguishable, and the surfaces were smooth. The urinary bladder was full, containing clear urine.

Conclusion of Safety Study

The method was confirmed to be safe for experimental animals, even at exposures 100 times higher than those intended for clinical use.

The sheath covering the probe prevents direct contact between the circulating fluid and the treatment surface, while ensuring efficient heat transfer to surrounding tissues. As a result, active hydro-hyperthermic treatment is maintained at 42 - 44°C throughout the experimental period. Experiments in rats demonstrated that this method is safe during both the treatment and subsequent observation periods.

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