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OUTLOOK FOR THE USE OF FOCUSED SHOCK WAVES AND PULSED ELECTRIC FIELDS IN THE COMPLEX TREATMENT OF MALIGNANT NEOPLASMS

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Abstract - **The experimental studies the synchronous action of electric field microsecond range with amplitude within the range of 1 7 kV/sm and shock waves with pressure before 100 MPa on permeability cells membranes of the mouses ascitic tumors in vitro have shown the intensification the efficiency of the forming the irreversible pores under synchronous action. Thereby, enabling the electric field in the compression phase of shock wave pulse can essential reduce the electric field intencity required for breakdown cells membrane. In usual condition at amplitude of electric field, specified above, electric breakdown membrane carries basically reversible nature. At the same time in the pressure field tension phase of shock-wave pulse reversible pores, created by electric field, can grow before sizes, under which wholeness membrane is not restored.**

Under simultaneous action on celluar suspension the shock wave and electric field with moderate intensity cells survival is redused in 5 once in contrast with occuring at different times action, and in 10 once in contrast with checking. The most sensitive to influence by under study fields are cells in phase of the syntheses DNA, preparation to fission and in phase of the mitosis.

Thereby, continuation of the studies on use synchronous action shock waves and pulsed electric fields in complex treatment of the tumors introduces perspective.

It is common knowledge that there are such forms of treating cancer as with high-intensity ultrasonic waves [3, 4] and focused shock waves [5]. The cytotoxic action of shock waves on cancer cells [2, 6, and 7] has been also described. The ability of focused shock waves alongside with mechanical damages of cells to break sulphide bonds and to produce reactive free radicals makes possible the participation of free radicals mechanism in changing membrane permeability of cells [2].

However, these forms are of restricted use owing to the development, under high negative pressure of the shock wave impulse, of cavitation processes within the wave fascicle that damage also healthy tissues and cause loss of efficiency of tumor growth suppression.

The disadvantages of the known forms of treatment can be removed by the offered new form of treatment of malignant neoplasms based on synchronous action of the focused shock wave impulse and pulsed electric field in the nanosecond or microsecond range in duration [1].

Theoretical and experimental studies of the electric breakdown of cell membranes during the last 25 years have proved that the action of a high-intensity electric field produces electromechanical instability that makes pores in cell membrane. When the intensity of the field is more than 20 кV/cm the breakdown is irreversible, and the cell stops functioning [8]. The same researches have also shown exponential voltage reduction of the breakdown of a cell membrane when the pressure rises [9].

On the basis of numerical calculations of electric fields in the cytoplasmic membrane and in the membrane of the cell nucleus induced by the external field, the expediency of using synchronous influence of the electric field in the nanosecond range and acoustic shock waves has been studied. The role of bubstons (charged microvesicles in a conductive liquid) in the formation of pores in a membrane has been also described.

The results of the experimental researches with regard to the influence of electric fields in the microsecond range with amplitude that varies between 1 and 7 кV/cm and of shock waves at pressure up to 100 MPa on the permeability of the membranes of ascetic tumor cells of mice in vitro have shown the efficiency rise of the formation of irreversible pores under their synchronous action.

Thus, applying the electric field during the compression phase of the shock-wave impulse allows considerably lowering the amplitude of the electric field intensity required for the breakdown of a cytoplasmic membrane.

Under ordinary conditions where the amplitude is that of the specified electric fields, the electric breakdown of the membrane is convertible. At the same time, under the pressure of the shock-wave impulse during the expansion phase the size of a convertible pore produced by the electric field can grow up to a size when the integrity of the membrane can not be restored.

Under simultaneous influence on the cell-rich fluid of the shock wave and the moderate intensity electric field, the cells survival rate is 5 times less than under alternative action, and 10 times less in comparison with the control parameters. The most sensitive to the influence of the

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subject fields are the cells during the phase of DNA synthesis, during preparation for the cell division and during the mitosis phase.

The experiments have used the original designs of electromagnetic generators of focused acoustic shock waves having adjustable space and time parameters of the shock-wave impulse in the focus zone. Further studies with regard to the use of the combined shock-wave impulse and electric impulse effect in therapy of tumors are expedient.

Concentration of the energy of acoustic shock waves in the area of a tumor inside the organism of a patient does not cause problems, since the soft tissues of the organism are acoustically transparent. This technique is well developed in lithotripsy. Specificity of the use of focused shock waves for exercising influence on a tumor has generally the same features as in lithotripsy. The shock wave can be focused in a volume that varies between 0.008 to 0.1 cm^3 both on surface-localized tumors and on deep-located ones, yet scanned influence within the tumor can be technically provided. Excitation in tissues and organs of strong electric fields localized in space on the contrary causes certain problem. Hereunder, in connection with the issue of the combined influence, three opportunities will be discussed: contact transcutaneous use of the electric field in the area of a tumor, noncontact inductive excitation of the electric field in the area of a tumor and excitation of high-frequency or super-high-frequency fields in the area of a tumor.

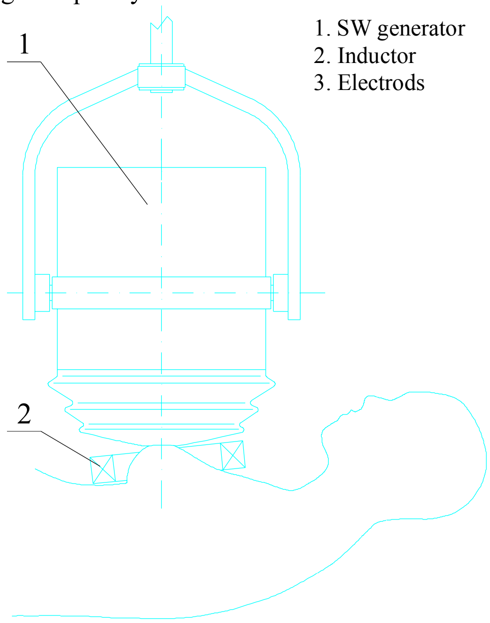

Fig.1

The localized influence of the electric field can be exercised when tumors are located close to the skin integument and in the extending parts of the body having restricted transversal sizes, for example, in the case of the breast cancer.

Figure1 shows the version of the combined influence using inductive excitation of the electric field in the area of a tumor. A coil is placed on the breast, which serves for discharging the condenser. The generator of shock waves 1 enters in acoustic contact with the organ, so that the shock wave is focused in the area of the tumor. The alternating magnetic field produced by the coil 2 induces into the tissues of the mammary gland the electric field, which intensity can be calculated on the base of the expression $E \sim \frac{\omega BR}{2}$, where

ω is frequency of the discharge

B is induction of the magnetic field

R is distance from the center of the coil

Having $\omega \sim 2\pi 10^6$, $B = 1$Tl, $R \sim 1$ to10 cm, and then electric fields having intensity of 0.3 to 3 кV/cm are excited. Taking into account the survival rate values with regard to the cells in vitro, therapeutic effect in vivo can be possible.

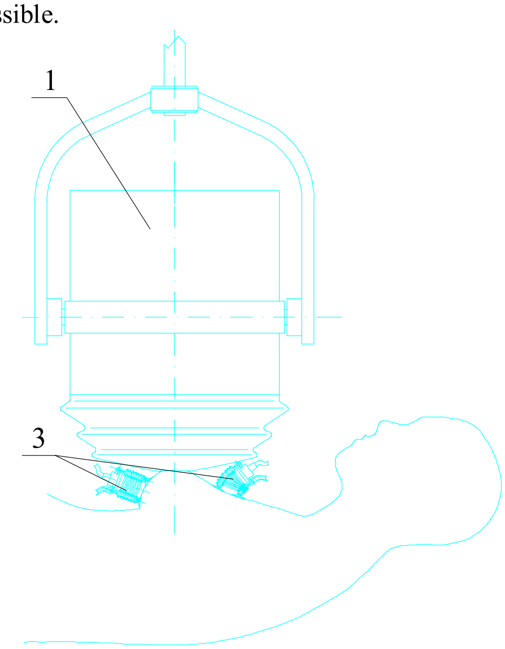

Fig.2

Figure 2 shows the version of the combined influence when the transcutaneous excitation of the electric field is produced in the mammary gland by electrodes of a special design 3, that have suckers and are filled by normal saline solution. In this case, the intensity of the field produced in the mammary gland is determined by the current applied to the electrodes and the distance between them $E \sim \frac{V}{l}$. When $V \sim 5$ kV and $l \sim 5$ cm, $E \sim 1$ kV/cm, i.e. it reaches values, which should assure therapeutic effect. For exception of side effects, the duration of the impulse should be chosen as short as possible, for example, in the microsecond range.

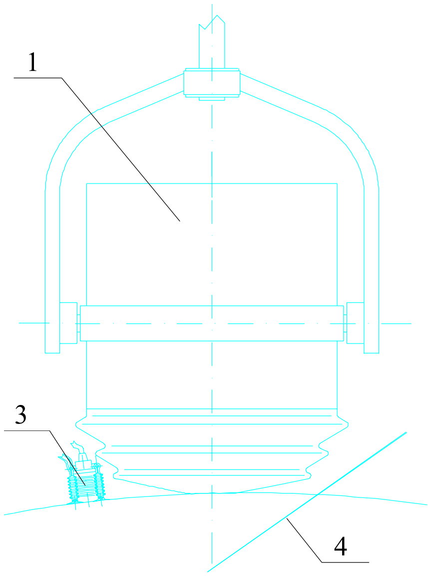

Fig.3

Figure3 shows the variant of the combined influence, when the excitation of the electric field in a subcutaneous tumor is provided using epicutaneous electrode 3 and electrode-needle 4 introduced into the tumor. The intensity of the electric field close to the electrode-needle is calculated on the basis of the expression E ~ $\frac{V}{R \ln \frac{d}{r_0}}$ where

R is distance from the axis of the needle

d is length of the needle

$2r_0$ is diameter of the needle.

When $R \sim 0.5$ cm, $d \sim 5$ cm, $r_0 \sim 0.1$ cm and $V \sim 3$ kV in the area 0.5 cm far from the needle, the intensity of the electric field makes E ~ 1.5 kV/cm.

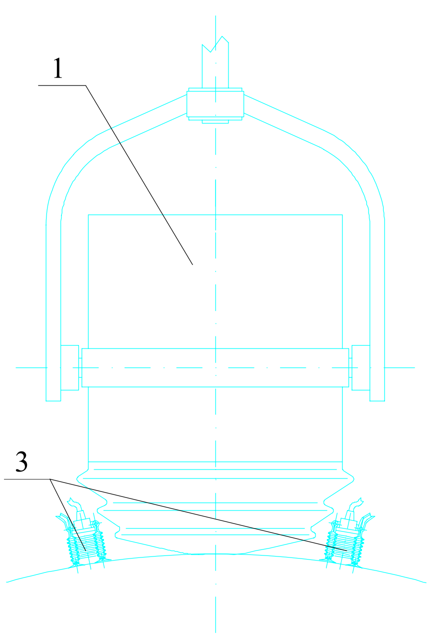

Fig.4

Figure 4 shows the variant of the combined influence on subcutaneous tumors by applying electrodes on the skin surface close to the tumor. In this case, a field of ~ 1 kV/cm intensity can be produced close to the skin surface.

In the version where the excitation in a tumor of the microwave field occurs during the combined influence, the waveguide aperture contacts with the lateral surface of the breast, and the shock wave is from above applied. Nowadays the technique of impulsive microwave oscillators allows producing close to the waveguide aperture fields of some kV/cm amplitude. Though the efficiency of the permeabilization lowers along with frequency rise, other factors like heating of the tissue in the microwave field, nonlinear effects connected with detecting features of the biological membranes can be here essential. The issue of using microwave fields for the combined influence requires additional studies.

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