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SHORT COMMUNICATION

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THE EFFECT OF ELECTROMAGNETIC FIELD AND LOCAL INDUCTIVE HYPERTHERMIA ON NONLINEAR DYNAMICS OF THE GROWTH OF TRANSPLANTED ANIMAL TUMORS

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Aim: **To examine the effects of electromagnetic field with amplified magnetic component and local inductive hyperthermia (IH) on nonlinear dynamics of the growth of animal tumors.** ***Materials and Methods:*** **Guerin carcinoma, Lewis lung carcinoma, sarcoma 45, Walker 256 carcinosarcoma and Pliss lymphosarcoma were studied. The animal tumors were exposed inside of loop aerial, 3 cm in diameter locally for 30 min. Parameters of electromagnetic irradiation (EI): frequency 40 MHz, magnetic intensity 72 A/m, electric intensity 200 V/m and the output power 50 W. The temperature measured by immersion of thermocouple inside the center of the tumor didn't exceed 38.5–39.5 °C. Nonlinear dynamics of the growth of animal tumors was analyzed by autocatalytic equation. The heterogeneity of ultrasonic image of the tumor was analyzed by Moran spatial autocorrelation.** ***Results:*** **The strongest inhibition effect under the influence of EI was in Pliss lymphosarcoma and sarcoma 45. The growth stimulation of animal tumors after EI was recorded in Walker 256 carcinosarcoma. The use of mild IH increased the blood flow in the tumor of Guerin carcinoma.** ***Conclusion:*** **These results are important for clinical application because they testify the necessity of optimization of schemes for local EI during anticancer neoadjuvant therapy with the use of drugs or magnetic nanoparticles. The use of mild IH as a basis for the monotherapy of malignant tumors is not expedient.**
Key Words: **inductive hyperthermia, animal tumors, blood flow, nonlinear dynamics.**

The electromagnetic field in radiofrequency range is widely used in hyperthermia induction of malignant human tumor for combined anticancer therapy. Malignant tumors have different sensitivity to electromagnetic fields that is partially transformed into the heat. Radiofrequency hyperthermia produces local heating (39–46 °C) of the tumors without generation of whole-body hyperthermia. The temperature in the center of the heated tumor fluctuates within ± 0.1 °C, while the temperature uniformity within the tumor fluctuates within ± 0.5 °C [1]. Recently scientists have demonstrated that the heating of rodent tumors up to 39–42 °C was accompanied by enduring increase in blood flow and oxygenation in the tumor [2].

One of the branches in hyperthermia known as electrohyperthermia is based on the transfer of electromagnetic energy into the tumor with the help of capacitive electrodes, that results in the depolarization and in the destabilization of cell membranes and change active membrane transport, the membrane capacity, potential, etc. The local electrohyperthermia treatment inhibits the growth of the treated tumors compared to the nontreated ones. However the control and treated groups had no differences in the life span, and only 10% of treated animals were cured [3, 4].

The second branch of hyperthermia uses the magnetic component of electromagnetic fields in the radiofrequency spectrum for the localization and the concentration of the heat during anticancer therapy or activation of susceptor material implanted in the tumor [5, 6]. The radiofrequency magnetic-loop inductive applicator was used for the treatment of patients with large sarcomas. One to five weeks treatment resulted in a significant tumor necrosis and the pain relief for some patients [7].

The magnetic component of electromagnetic field causes heating in tumor tissues through induced eddy currents, which can initiate adverse effects during the treatment too. This paper examines the effects of electromagnetic field with amplified magnetic component and local inductive hyperthermia (IH) on nonlinear dynamics of the growth of animal tumors.

Experimental animals. 80 male rats with a body weight of 110 ± 20 g (bred in Institute of Oncology, AMS of Ukraine, Kyiv, Ukraine) and 20 C57BL/6 male mice with a body weight of 19 ± 1 g (bred in A.A. Bohomolets Institute of Physiology, NAS of Ukraine, Kyiv, Ukraine) were used. Animals were housed in 2 groups: group 1 — control (no treatment); group 2 — irradiation (40 MHz). All animal experiments in this study were approved by the regional animal ethic committee.

Tumor transplantation. The transplantation of Guerin carcinoma, Lewis lung carcinoma, sarcoma 45, Walker 256 carcinosarcoma and Pliss lymphosarcoma were performed according to the established procedure.

Electromagnetic irradiation. We used the first prototype of device for medical treatment called "Magnetotherm" (Radmir Co., Ukraine) [8]. The animal tumors were exposed inside of loop aerial 3 cm in diameter locally for 30 min. Parameters of electromagnetic irradiation (EI): frequency 40 MHz, magnetic intensity 72 A/m, electric intensity 200 V/m and the output power 50 W. Irradiation treatment was started from the 4th day and then performed on the 6th, 8th and 10th days after tumor transplantation. The temperature was measured by immersion thermocouple CH-1 (Metalphysics, Ukraine) in the center of the tumor. Tumor temperature did not exceed 38.5–39.5 °C.

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Abbreviations used: EI – electromagnetic irradiation; IH – inductive hyperthermia.

The analysis of nonlinear kinetics of tumor volume. Nonlinear kinetics of tumor volume was evaluated by growth factor φ according to autocatalytic equation. The duplication time T_c of tumor volume for control group and T_{EI} for group after EI was determined according to [9].

The effect of electromagnetic field and local IH on nonlinear dynamics of the growth of animal tumors was evaluated with the braking ratio:

$$\kappa = \frac{\varphi_c}{\varphi_{EI}}, \qquad (1)$$

where φ_c — is growth factor for control group of animals, φ_{EI} — is growth factor for group after *EI*.

Analysis of Ultrasound Image. Ultrasonic studies were done by ultrasonic device ATL HDI 3000 (Fillips, USA), we also used a transducer with frequency of 6 MHz.

The heterogeneity of tumor structure. The heterogeneity of ultrasound image *G* was evaluated with spatial autocorrelation statistics *r* by Moran [10]:

$$G = 1 - r. \qquad (2)$$

The analysis was performed with the MATLAB 7.0 (©1984–2004 The MathWorks, Inc.) software.

Statistics. Statistical processing of numerical results was carried out using Statistica 6.0 (© StatSoft, Inc. 1984–2001) computer program with parametric Student's *t*-test.

As it is shown in the Table, the growth kinetics of animal tumors had very different nonlinear responses under the influence of electromagnetic fields with amplified magnetic component and local IH. The strongest inhibition effect under the influence of EI was in Pliss lymphosarcoma and sarcoma 45. The growth stimulation of animal tumors after EI was recorded in Walker 256 carcinosarcoma. Nonlinear dynamics of tumors' growth was different for each single animal in all investigated groups.

Table. The growth kinetics of animal tumors

№	Tumor	Parameters				
		T_c (h)	T_{EI} (h)	φ_c (day^{-1})	φ_{EI} (day^{-1})	κ
1	Guerin carcinoma	12.32	12.05	0.45 ± 0.01	0.46 ± 0.05	0.99
2	Lewis lung carcinoma	14.22	15.40	0.39 ± 0.02	0.36 ± 0.01	1.07
3	Sarcoma 45	9.24	12.32	0.60 ± 0.03	0.45 ± 0.01*	1.31
4	Walker 256 carcinosarcoma	9.24	8.40	0.60 ± 0.01	0.66 ± 0.01*	0.91
5	Pliss lymphosarcoma	13.20	17.33	0.42 ± 0.02	0.32 ± 0.01*	1.32

*Statistically significant difference from control group.

The ultrasonic studies were used for interpretation of peculiarities in tumor blood flow during EI. Guerin carcinoma was researched only because there were problems in visualization of ultrasound images on the monitor for other experimental tumors. Figure shows the sonogram of Guerin carcinoma on the 10th day after tumor transplantation before and after EI. The sonograms show that tumor heterogeneity parameter *G* for Guerin carcinoma after EI was higher by a factor of 2.9 than that in non-irradiated tumor. This is in accordance with well known medical observations that EI and mild hyperthermia is characterized by intensive tumor blood flow [2].

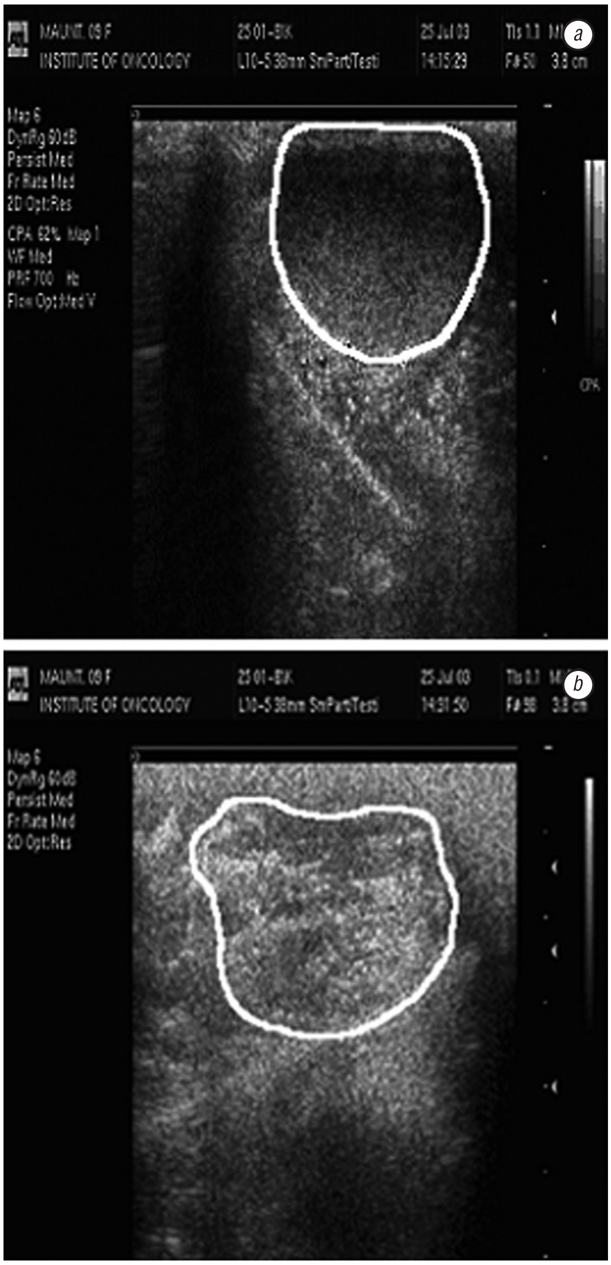

Figure. The sonogram of Guerin carcinoma and tumor heterogeneity parameter *G*: *a* — without EI (*G* = 0.24); *b* – after 15 min EI (*G* = 0.69)

According to the presented data, one may suppose that recorded effects of inhibition or stimulation of the growth of animal tumors after electromagnetic stimulation may be caused by peculiarity of vascular damages in different experimental tumors. These results are important for clinical application of medical technologies because they testify against the use of mild IH as a basis for the monotherapy of malignant human tumors and the necessity to facilitate local EI during anticancer neoadjuvant therapy with the use of drugs or magnetic nanoparticles. In general, the application of local hyperthermia in clinical oncology is effective when combined with chemotherapy or radiochemotherapy as shown in [11].

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ВЛИЯНИЕ ЭЛЕКТРОМАГНИТНОГО ПОЛЯ И ЛОКАЛЬНОЙ ИНДУКТИВНОЙ ГИПЕРТЕРМИИ НА НЕЛИНЕЙНУЮ ДИНАМИКУ РОСТА ПЕРЕВИВНЫХ ОПУХОЛЕЙ ЖИВОТНЫХ

Цель: **изучить влияние электромагнитного поля с повышенной магнитной компонентой и локальной индуктивной гипертермией на нелинейную динамику роста перевивных опухолей животных.** ***Материалы и методы:*** **в работе использовали карциному Герена, карциному Льюис, саркому 45, карциносаркому Уокера 256 и лимфосаркому Плисса. Опухоли животных облучали локально на протяжении 30 мин внутри рамочной антенны диаметром 3 см. Параметры электромагнитного облучения: частота — 40 МГц, напряженность магнитного поля — 72 А/м, напряженность электрического поля — 200 В/м и выходная мощность — 50 Вт. Температура, измеренная погруженной в центр опухоли термопарой, не превышала 38,5–39,5 °С. Нелинейную динамику роста опухолей животных анализировали с помощью уравнения автокатализа. Гетерогенность структуры ультразвуковых изображений оценивали с помощью модифицированного коэффициента пространственной автокорреляции по Морану.** ***Результаты:*** **наибольший эффект торможения роста под влиянием электромагнитного облучения был у лимфосаркомы Плисса и саркомы 45. Для карциносаркомы Уокера 256 регистрировали стимуляцию роста опухолей животных после электромагнитного облучения. Использование умеренной индуктивной гипертермии усиливало кровоток в карциноме Герена.** ***Выводы:*** **полученные результаты важны для клинического применения, так как они свидетельствуют о необходимости оптимизации схем локального электромагнитного облучения во время противоопухолевой неоадъювантной терапии с применением препаратов или магнитных наночастиц. Использование умеренной индуктивной гипертермии как базовой монотерапии злокачественных опухолей нецелесообразно.**

Ключевые слова: **индуктивная гипертермия, опухоли животных, кровоток, нелинейная динамика.**