FACILITY DEVELOPMENT FOR A COMBINED CANCER THERAPY

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The system for local hyperthermia of cancers was simulated. This system is based on independently phased dipoles with frequency 150 MHz. The electromagnetic field distributions are calculated in cut of tissue-equivalent phantom. It was shown that the electromagnetic field can be focused in desirable volume by means of independent vary of amplitude and phase of each dipole. The advantages of combined therapy are discussed for common using of hyperthermia with chemotherapy, radiation therapy or surgery.

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1. INTRODUCTION

Surgery, chemical therapy and radiation (gamma, electron or hadron) are three classical methods of the cancer treatment. They are used independently and in combination one another. But all tree methods have some limitation and negative after effects for patients. The decrease of such negative effects is one of main direction of contemporary oncology.

So called hyperthermia (ancient Greek ὑπερ- – «excessively» and θέρμη – «heat») is one of possible methods to decrease negative after effects. The hyperthermia is kind of thermotherapy based on increasing temperature of body, body part or organ prone to pathological process. It was shown that combined chemical therapy and hyperthermia is very perspective because the medical preparation dose can be 2-3 times reduced [1-4]. Some types of cancer cells can be made more sensitive to the radiation using hyperthermia also. Developing and adoption of treatment methods when intensification chemotherapy effect takes place, in clinical practice is a primary target. The thermal effect lead to lysosome activation, tissue breathing and protein synthesis inhibition, tissues pH decreasing, kariokynetic cycle modification, trans membrane transfer improvement, sensitization tumor cells to chemotherapy and growing up immunity. The temperature when volume blood flow in healthy tissues decreases as a result of progress disseminated intravascular clotting is the limit of the thermotherapy usage. The hyperthermia is conventionally devisable into three temperature ranges:

- 43…44°C – direct destruction of tumor;
- 40…42°C – sensitization tumor cells to chemotherapy or radiotherapy;
- 38…40°C – tumor size increasing is possible.

Indeed, patient's heating to 44°C can lead to a number of pathological changes and progress of fatal complication. That's why the temperature 44°C during local hyperthermia is not reached yet. The heating mode 41.5…42.1°C during 60…120 min are more often applied. There are several types of hyperthermia and respectively several frequencies range:

- Overall hyperthermia (10…15 MHz);
- Regional hyperthermia (40…100 MHz);
- Local, distant, intracavitary hyperthermia (100…200 MHz, 433 MHz, 915 MHz, 2.5…3 GHz);
- Combined hyperthermia (overall + local);
- Extra high frequency (EHF) therapy (30…300 GHz).

Several heat-transfer materials (water, air) are used for overall hyperthermia in practice medicine. In that case the greatest temperature is reached on the body's surface that leads to a burn.

2. HYPERTHERMIA COMBINED WITH RADIOTHERAPY

There are a lot of works, where the synergism of hyperthermia and radiation effect on cancer's growth is shown. It is assumed that modification effect of hyperthermia on radiation's effect consists of next points [5]:

1. Radiation's sensitivity increasing;
2. Decreasing of cell's ability to regenerate sublethal and potential lethal damage;
3. Selective influence to cells which are in radioresistance phase of kariokynetic cycle.

Blood flow increases with hyperthermia which leads to tissues saturation growth by oxygen and, consequently, to higher sensitivity of cancer to the radiotherapy. Radiosensitization's effect of hyperthermia is depended of sequence of heating and radiation application: the greatest effect is reached at their simultaneous application. If radiotherapy precedes hyperthermia, regeneration of radiation damages will take place at interaction with thermal damage. If hyperthermia precedes radiotherapy, regeneration of thermal damage will takes place at interaction with radiation damage. The correlation between this phenomenon and value of unprepared filamentous DNA rupture was shown [6].

3. HYPERTHERMIA COMBINED WITH CHEMOTHERAPY

Hyperthermia and anticarcinogenic chemotherapeutic medicine can acts independently, can supplement each other and perfectly cooperate. The major mechanisms which provide anticarcinogenic chemotherapeutic medicine's effect are the raised concentration of drug in a tumor. The concentration raise is a result of increasing blood supply and permeability of membranes, and also an increasing endocellular medicinal metabolism and reaction acceleration.

There are four groups of chemical compounds which antineoplastic effect in the conditions of a hyperthermia is studied [7]. Drugs with linear cytotoxicity increasing versus of the temperature rise make the first group: alkylating agent (thiophosphamide), bifunctional alkylates (nitrosourea), mitomycin, cisplatin. A limit cytotoxicity

is proportional to the temperature for second group drugs. The accurate synergism of hyperthermia and chemotherapy appears for the temperature higher than 42…43ºC. For example it is observed for adriamycin, bleomycin and actinomycin D. Third group consists of drugs which become cytotoxic only at high temperature (cystamine, amphotericin B). Drugs which have the constant cytotoxicity at temperature 37…45ºC (methotrexate, fluorouracil, vincristine, and vinblastine) can be placed to the forth group.

4. RADIOTHERAPY AND COMBINED THERAPY IN RUSSIAN ONCOLOGICAL SCIENTIFIC CENTER

Combined therapy using the radiotherapy with the hyperthermia Thermo Radio Therapy, TRT) in RORC is spent since 1980. TRT was carried out more than 1000 patients at present.

The improved results of TRT in comparison with conventional radiotherapy (RT) are presented in Table 1. The frequency of full regresses of localizations listed above is higher after TRT. Result's analysis shows that the five-year survival rate after TRT is higher than after radiotherapy (Table 2).

Table 1

Frequency of full regression after radiotherapy or thermoradiotherapy courses

Tumor's localization	TRT, %	RT, %	Statistic error
Prostate cancer	94±2.3	69±8.2	p<0.05
Soft tissue sarcoma	45±5.2	14±5.1	
Regional metastasis of neck epidermoid cancer	57±6	12±7.8	
Epidermoid anal channel cancer	100	60±21.9	
Extraabdomenal desmoids cancer	33±7	0	
Relapse rectum cancer	24±6.3	5±4.9	

The TRT treatment program is realized in RORC. Such program allows to sufficient and authoritative reduce of the regional cancer recrudescence and metastases comparatively to the surgery or independently radiotherapy. As an example, the rectum cancer recrudescence was observed for 0.9±0.6 % (2 form 220 patients) and metastases for 5 % (11 from 220 patients) comparatively with 16.2±1.9 % (64 form 395) for surgery and 9.6±2.1 % (26 from 272) for surgery and before RT.

Table 2

Five-years survival rate after radiotherapy or thermoradiotherapy courses

Tumor's localization	TRT, %	RT, %	Statistic error
Prostate cancer	68±4.5	53±8.0	p<0.05
Soft tissue sarcoma	46±5.2	35±7.0	
Regional metastasis of neck epidermoid cancer	24±4.2	9±4.6	
Epidermoid anal channel cancer	69±6.8	30±12.7	
Extraabdomenal desmoids cancer	40±5.7	6±4.5	
Relapse rectum cancer	68±4.5	53±8.0	p<0.01

Indeed, the efficiency of TRT was shown for a number of cancer types in RORC. The local heating with 41…45ºC temperature regime and 60 minutes duration is improved the RT results because of the cancer cells damage and radio sensitization. Cancer treatment effect grows versus temperature and procedure time increasing.

5. HYPERTHERMIA FACILITIES AND FREQUENCY RANGE CHOICE

Facilities for overall and regional hyperthermia are manufacturing by some companies since 1980's [8-10]. Federal state unitary enterprise "Research & production corporation "Istok" is the main manufacturer in Russia. The local hyperthermia became more useful as whole body hyperthermia at present. The local hyperthermia allows to focus the radiation in the local volume placed deep inside into human body and to prevent of other tissues or organs heating.

Microwaves application is more perspective in comparison with optical and infrared waves because they having higher penetrating capacity in the human body perspective in the field of a hyperthermia. The RF frequency range (100…200 MHz) is optimal because the wavelength in human body will approximately equal to the body's size. Dielectric properties of biological tissues at 150 MHz are shown in Table 3 [11].

Table 3

Dielectric properties of biological tissues in 150 MHz range

	ε	ρ, g/cm^3	σ, S/m
Muscle	62.8	1.047	0.72
Bone	14.6	1.99	0.068
Skin	63.5	1.125	0.53
Blood	72.2	1.058	1.25
Tumor	74	1.047	0.89
Fat	5.84	0.95	0.037

The blood is the most conductive tissue but blood intravascular clotting can not be a serious problem due to the blood flow. Dielectric properties of cancer are comparable with muscle's one (they have same density, similar values of conductivity and relative permittivity). It's should be taken into account at planning of the hyperthermia procedure in order to decrease damage effects on healthy tissues. Fat and bones have a less conductivity in comparison with muscle and tumor.

Now some USA, Germany and Netherlands companies are offer a number of local hyperthermia facilities but its price is very high (up to 8 MEuro).

6. DIPOLE SYSTEM FOR LOCAL HYPERTHERMIA

The antenna grid consisting of number independently phased dipoles is proposed for local hyperthermia of cancers. The operating frequency is chosen equal to 150 MHz in R&D. The dipoles proposed are modification of well-known half-wave dipoles. The grid will consists of an array of such dipoles and hold on the cylindrical surface with diameter equal to 40 cm. Dipoles fed independently by coax cable (for instance low loss cable as RG213) from amplifiers at frequency 150 MHz. Inde-

pendent feeding is necessary to focus electromagnetic fields in local region. The focusing can be done by independently operation phase and amplitude choice for each dipole in the grid. The tissue-equivalent phantom and heating dipoles grid are shown in Fig.1.

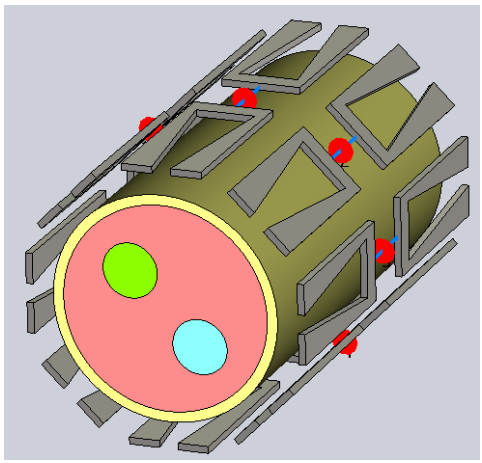
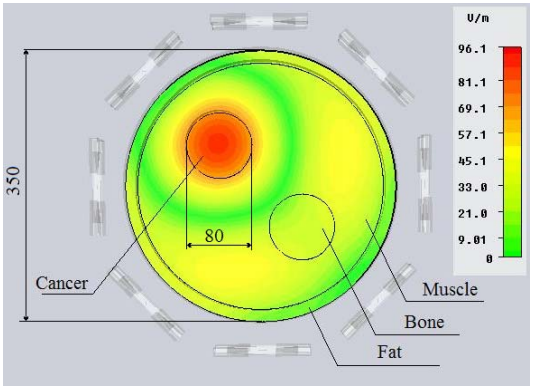
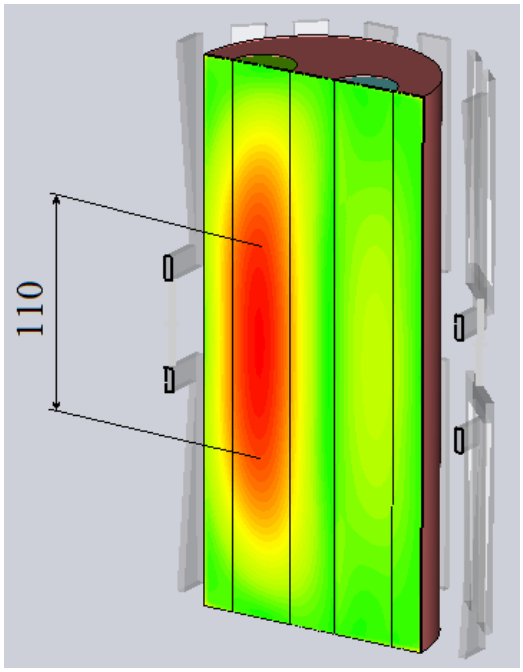


Fig.1. Tissue-equivalent phantom and dipoles grid

Distributions of EM field in transverse (a) and longitudinal (b) cuts of heating model are presented in Fig.2.



a



b

Fig.2. Electric field distributions in cuts of heating model: a – transverse cut; b – longitudinal cut

It is clear, that the electric field maximum is located in the center of the tumor. It was reached by means of an especial choice of phase and amplitude values of the RF field in each dipole as it was noted above. The electric field distribution versus time (or RF field phase) is shown in Fig.3. The transversal size of heated spot (where electric field decreases in $\sqrt{2}$ times) is equal ~7…8 cm, and the longitudinal size is equal ~10…12 cm. In other words, heating volume is a volume of cylinder with a radius ~4 cm and length ~10 cm.

The specific absorption rate (SAR) can be calculated if the electric field distribution in phantom is known. SAR is the measure of the rate energy which is absorbing in the body when in is irradiating by RF electromagnetic field. It is defined as the power absorbed per mass of tissue. SAR can be calculated f as:

$$SAR = \frac{\sigma \vec{E}^2}{\rho} \text{ [W/kg]}, \quad (1)$$

where σ is the electrical conductivity; E is the RMS electric field; ρ is the phantom density.

Also we can calculate the rate of temperature increasing in the tissue, if specific heat c_i is known:

$$SAR = c_i \frac{dT}{dt}. \quad (2)$$

Eq. (2) is rewritten taking no account the blood flow. SAR is equal 235.5 W/kg with RMS supply power of each dipole equal 60 W. This implies that some minutes will necessary to heat tumor to 8 K (the tumor heat capacity is equal to 3560 J kg^{-1} K^{-1}). At the same time the temperature of healthy tissues will increases no more then 2.5 K.

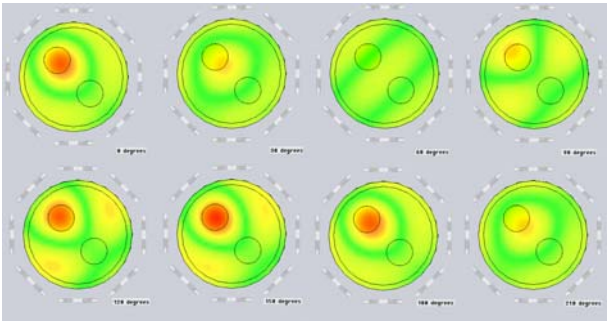


Fig.3. Electric field distribution versus time (or RF field phase)

7. RF POWER FEEDING SCHEME

As it was noted above, the RF power supply should be independed for each dipole. The RF power system schematic layout is shown in Fig.4: 1 – driving generator with input signal's frequency range 100…300 MHz and input impedance 50 Ohm; 2 – 8-out power splitter (for example Mini-circuits ZBSC-8-82+); 3 – voltage-controlled phase shifter (Mini-circuits JSPHS-150) with frequency range 100…150 MHz, phase range 180°, control voltage 0…12 V; 4 – solid state amplifier (Mitsubishi RA60H1317M1A-101) with frequency range 135…175 MHz, output power – 60 W, supply voltage – 12.5 V, control GAP-pin voltage 12.5 V; 5 – RF dipole's grid.

The operating principle of such layout is the following. The signal from driving generator has the constant frequency and splits into 8 channels. Then by means of controlled 8 phase shifters and 8 solid state amplifiers

we can adjust phase and amplitude of every signal. Due to these adjustments electric field focusing in the desire region is available.

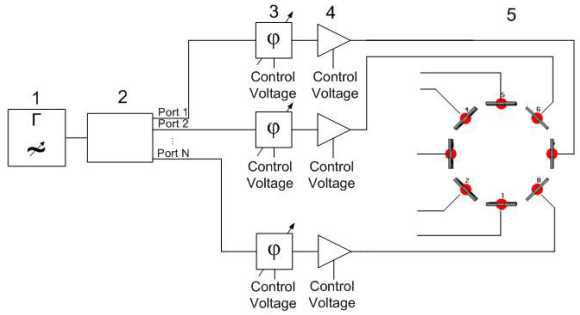


Fig.4. RF power system schematic layout

Modern solid state amplifiers can derive the necessary amplification and are simple and stable at operation. For example, solid state RF amplifier Mitsubishi RA60H1317M with amplify frequency range of 135…175 MHz and supply voltage 12.5 V can be used to provide the necessary RF power (to 60 W) and SAR values. The control of RF power can be realized using amplifier's GAP channel which provide the turn on/off of amplifier.

Indeed the 8 dipole antenna grid should be controlled by 16 voltage signals (8 for amplifiers and 8 for phase shifters). The low-voltage control system connected to PS should be designed future.

CONCLUSIONS

Combined therapy using the hyperthermia with the radiotherapy of the chemotherapy is very perspective methods of the cancer treatment. The efficiency of combined therapy is evaluated on practice. The local hyperthermia became more useful as whole body and regional hyperthermia at present. The array of half wave dipoles is proposed for local hyperthermia. It was shown that the localization of heating in ~ 4×10 cm volume can be realized using this scheme. It was calculated that some minutes is necessary for tissue heating on 8 K (from 36.6 to 44°C) with 60 W of RF power in each dipole.

A number of problems should be solved before introducing the facility in the clinical trials:

1. 3D-models of body should be done using MRI and PET-CT scanning and correct tissue model should be simulated. In other words, after determining of tumor localization by means of scanning, it is necessary to simulate the computer model in which all tissues will be marked out. It is necessary because all tissues have personal dielectric properties. The thermodynamic problem should be solved using 3D model of RF field.
2. Software for fast 3D simulation of electromagnetic fields distribution should be developed. This software should include the heating process simulation.
3. Correct and low traumatic methods of temperature control are necessary.

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РАЗРАБОТКА УСТАНОВОК ДЛЯ КОМБИНИРОВАННОЙ ТЕРАПИИ ОНКОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЙ

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Проведено моделирование работы системы для локальной гипертермии онкологических заболеваний на основе системы независимо фазируемых дипольных излучателей, работающих на частоте 150 МГц. Получены картины распределения электрических полей в сечении облучаемого образца (тканеэквивалентного фантома). Показана возможность фокусировки электромагнитного поля в необходимом объеме за счет независимого изменения фазы и амплитуды излучения каждого из диполей. Рассмотрены перспективы комбинированного использования гипертермии и химической или лучевой терапии и хирургии.

РОЗРОБКА УСТАНОВОК ДЛЯ КОМБІНОВАНОЇ ТЕРАПІЇ ОНКОЛОГІЧНИХ ЗАХВОРЮВАНЬ

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Проведено моделювання роботи системи для локальної гіпертермії онкологічних захворювань на основі системи незалежно фазіруємих дипольних випромінювачів, що працюють на частоті 150 МГц. Отримано картини розподілу електричних полів у перерізі опромінюваного зразка (тканееквівалентного фантома). Показана можливість фокусування електромагнітного поля в необхідному об'ємі за рахунок незалежної зміни фази і амплітуди випромінювання кожного з диполів. Розглянуто перспективи комбінованого використання гіпертермії та хімічної або променевої терапії та хірургії.