Facility for thermoradiotherapy of deep-seated tumors

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Abstract. Therapeutic hyperthermia in combination with radiotherapy which is realized by means of modern linear electron accelerators (called thermoradiotherapy) is one of widely used contemporary cancer treatment methods. Hyperthermia provides increasing of the tumors sensibility to radiation. Thus the radiation dose could be decreased. The experience achieved at N.N. Blokhin Russian Cancer Research Center during 40 years shows that 5-year survival rate increases (15-40%) for a number of cancer types and localization. High dose can be easily delivered to the deep seated tumors but local heating is a big problem so far. One possible way to solve the problem of deep tissues local heating is discussed in this article, the brief review of previous simulations and latest results for experimental prototype setup are presented.

1. Introduction

Hyperthermia is an adjuvant methods of cancer treatment in which tumor temperature is increased to high values (40-44 °C). Many researches have shown that high temperature can damage and kill tumor cells, thus reduces tumor size. However the main advantage is that hyperthermia is a promising approach to increase efficiency of chemotherapy or radiation therapy. Under hyperthermia some tumor cells become more sensitive to the radiation and anticancer drugs. The effect on surviving fraction depends both on the temperature increase and on the duration of the expose. The main mechanism for cell death is probably protein denaturation at temperatures above 40 °C, which leads to changes in molecular structures such as cytoskeleton and membranes, and changes in enzyme complex for DNA synthesis and repair [1]. Heat also enhances the cytotoxicity of X-rays. Increased cytotoxicity is maximized when radiation and hyperthermia are given simultaneously. The combined effect decreases with time when the treatments are separated by more than one hour [2]. When cells are exposed to increased temperatures to anticancer drugs, their response is often different from the one at normal temperature. Drugs whose rate-limiting reaction is primarily chemical are expected to be more efficient at higher temperatures. Thus the combination of chemotherapy with hyperthermia has high potential in clinical practice [3].

The thermal therapy combined with the radiation (thermoradiotherapy, TRT) has been applied in N.N. Blokhin Russian Oncological Research Center (RORC) since 1980th [4]. More than 1000 patients have been treated to date. Such program allows to sufficient and authoritative reduce of the regional cancer recrudescence and metastases comparatively to the surgery or independently radiotherapy (RT). 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 $16,2\pm1.9$% (64

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from 395) for surgery and 9,6±2,1% (26 from 272) for surgery and before radiotherapy [4]. Frequency of full regression after TRT also increased: for prostate cancer form 69±8.2 % for RT to 94±2.3 % for TRT, for soft tissue sarcoma form 14±5.1 to 45±5.2 %, for regional metastasis of neck epidermoid cancer from 12±7.8 to 57±6 % etc. [5].

2. Problem of local heating of a deep seated tissues

Several hyperthermia systems have been proposed, however non-invasive heating of deep seated tumors is still a difficult technical challenge. In this case the electromagnetic (EM) fields have an advantage over other methods such as ultrasound: radio frequency (RF) fields have a greater penetration rate than optic or infrared waves. Single applicators are not effective in treating tumors located deeper than 2-3 cm. First applicators were not able to steer and focus energy without shifting patient position relative to the radiator. In these initial studies 27 MHz ridged waveguide [6], 70 MHz coax TEM-applicators [7] and 82 MHz helix [8] were used. Several applicators based on dielectric filled waveguide or horn antennae have been investigated for many years. In most cases, those devices produce an EM field distribution with maximum field intensity at the surface and in the center of the applicator. The intensity of the EM fields is rapidly falling off with both depth into tissue and transverse distance from the applicator center. To overcome these limitations the feasibility of using microstrip technique was investigated. For instance, spiral microstrip antenna were designed and integrated into applicators suitable for clinical use [9]. Because of their small size these antennas can be arranged into the arrays. They operate over the range of 400 MHz to 1200 MHz and produce sufficient specific absorption rate (SAR) distribution at a depth of few centimeters from the surface [10].

One of the major problems of the devices mentioned above is the limited depth of penetration due to the principle of skin-effect. Only tumors located 2-3 cm (7-8 cm for the contact flexible microstrip applicator [11] from the surface can be heated by these applicators. To increase SAR value in the tumors situated deeper than 10 cm relative to the surface SAR value it is necessary to focus energy of electric fields produced by an array of applicators. It consists of several antennae surrounding the patient and emitting radio-waves. Single antenna or groups of antennae are fed separately. Thus by proper selection of amplitudes and phases the interference patterns of the produced fields can be focused to create desirable temperature distribution [5]. Significant research successes have been obtained for the deep hyperthermia with the phased array. Simulation and measurements results are presented in [12].

RORC clinical studies demonstrate improving results of treatment by combined using of hyperthermia and radiation for the several tumor localizations. But only applicators for superficial hyperthermia were used in RORC. Common RORC-MEPhI-JINR project is pointed to expand the range of utilizing devices, i.e. using of devices for the regional hyperthermia gives more advantages for an oncological disease treatment.

3. Prototype of the local termoradiotherapy system

The most evident approach is using an annular array of applicator situated around the patient body [13]. Top view of this structure is shown in the figure 1. Arrays of applicators with variations in frequency, phase, amplitude and orientation in space give more possibilities to control heating pattern during hyperthermia treatment [12]. RF power feeding scheme is presented in [14]. Thus the phased array provides deeper tissue penetration of electromagnetic waves in comparison with single applicator, reduce undesirable heating of healthy tissues situated between applicator and tumor and improve local control for heating area. Also using array of applicators gives ability to control and to plan heating process without changing of patient position. Suggested phased array consists of eight copper dipoles, attached on the inner side of the dielectric cylinder, and surrounds a patient body. The aperture radius is up to 60 cm which can be applied in more cases. Dipoles are fed independently permitting to control phases and amplitudes of waves. Space between dipoles and the patient body is filled by deionized water (conductivity $\sigma \approx 0.001$ S/m). Thus applicators are squeezed from the inner

side by lossy medium with high permittivity (deionized water ε≈80), and from the outer side by medium with low permittivity (air ε=1). The conducting elements of antenna are isolated from lossy medium by thin layer of an insulator (thickness h≈1 mm). Because of energy density of electrical fields ($\vec{E}\vec{D}/2$) inside the dielectric tank is higher by a factor of ε (the relative dielectric constant of medium), energy is mainly concentrated inside the array. Thus deionized water not only cools body surface and superficial tissues but is also a matching medium. Electric field lines inside the phased array are parallel to the axis of dipoles. That's why heat absorption in the surface and superficial tissues (such as skin and fatty tissue) which is proportional to tissue conductivity (σ, these values for fat and skin are significant lower than for muscle or tumor tissue) will be substantially lower than in deeper tissues. Thus skin and fatty tissue overheating is reduced in comparison with the using capacitive applicators. So E_z (z is direction along of the patient body) is the only component, which may be able to control by shifting the amplitudes and phases of eight dipoles. Ex and Ey components are not under control. E-field generated by each of the dipoles is given by $E_j = A_j E_{j,0}(x,y) \cdot \exp(-i(\omega t - \Phi_j))$, where $E_{j,0}$ – is the complex E-field for A_j=1, Φ_j=0, and A_k=1 for $j{\neq}k$, A_j – is a scaling factor of amplitude, Φ_j – wave phase, j and k are numbers of dipoles, i is imaginary unit. It is possible to move peak of interference pattern and to focus it into the tumor site with the variation of these two parameters (phase and amplitude). The measure of the rate at which energy is absorbed by the body when exposed to a radio frequency (RF) electromagnetic field is a Specific Absorption Rate (SAR). It is defined as the power absorbed per mass of tissue and has units of watts per kilogram (W/kg): $SAR = (\sigma \vec{E}^2)/\rho$, ρ – is the density of the tissue (kg/m3), E – is the root of mean square electric field.
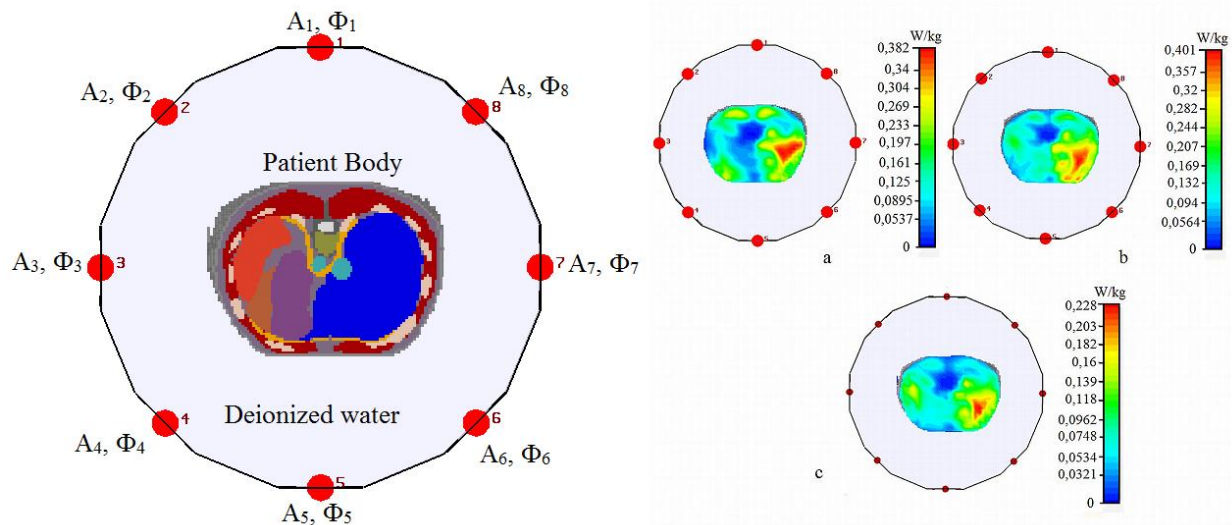

Figure 1. Top view of phased array surrounding patient body (left) and cross-section patterns of the SAR distribution with different operation frequencies (a) 150 MHz; (b) 100 MHz; (c) 80 MHz and with input phases of 50°, 50°, 50°, 50°, 0°, -30°, -40°, -10° applied to channels 1, 2, …, 8 respectively.

The simulations are performed with CST Microwave Studio which uses the Finite Element Method (FEM) for Maxell's equation solving. Their solvers feature curved elements of arbitrary order. These elements enable a conformal representation of the geometry which improves the simulation accuracy. In combination with the unstructured FEM grid, which can resolve small structure details very efficiently, it can increase the simulation performance dramatically. All simulations were performed for input rms power 0.5 W per each channel. To demonstrate that the phased array can produce a maximum SAR distribution inside patient body, electromagnetic simulations were performed at different operating frequencies. The voxel model which was used is presented in [15]. This model

doesn't contain tumor tissue. Material properties for water bolus, enclosure and antennae are also included in simulation. The blood flow and the thermal conductivity aren't factored in the simulation, thus the simulated pattern of SAR distribution have local maximum within vessels. The real SAR distribution hasn't these locals.

There are three operating frequencies were used for SAR simulation: a) 150 MHz, b) 100 MHz, c) 80 MHz. Cross-section patterns of SAR distributions with relative phases are depicted on Fig. 1 also. The simulated focus is steered to the liver with input phases of 50°, 50°, 50°, 50°, 0°, -30°, -40°, -10° applied to channels 1, 2, …, 8 respectively. Also the goal was to prevent occurring hot spots in other regions and to maximize the SAR value in relative to the SAR of healthy tissue. The phases were chosen manually by the principle that the peak SAR shifts away from the dipole which has phase delay, i.e. the peak SAR will shift away from the dipole #3 due to the phase delay on this dipole will be 50°. Amplitudes were not varied. Three operating frequencies mentioned above were used. It is clear that variation both amplitudes and phases leads to further localization of the heating region comparatively phases variation only as it was realized in [13].

4. Experimental results

Based on previous simulations [16] and RF feeding system design [14] the first experimental prototype was developed and constructed. It consists of two RF dipoles and one feeding system. Series of local heating experiments were done using such prototype. Experimental demonstration of the local energy distribution maximum and its motion versus of phase and amplitudes variation were the main goals of such experiments. Two dipoles were mounted on external side of a dialectical cylinder which was filled by deionized water. The tissue-equivalent phantom was prepared using a number of thin-walled dielectric tubes filled by salt water which permittivity and conductivity are close to human tissues. Tubes were placed on line connects centers of RF dipoles. Such phantom correctly imitates the deep suited tissue and can be easily used in temperature control which was organized by means of a number of thermocouples which were placed into all thin-walled tubes. The initial temperature was constant for all system points. Water starts the energy absorption after RF power on and the temperature in the local heating volume starts growth. Temperature distributions after heating are shown in figure 2 for in-phase dipoles on (a) and for 60 degrees phase shift (b). The heating was provided 20 minutes for in-phase experiments and 12 minutes for experiments with phase-shift. Zero-point on x-axe corresponds to the center of main cylinder. It is clear from figures that 50 mm of localization can be achieved in hyperthermia system proposed. Experimental heating results are compared with CST Studio Suite simulations (dot curves in figure 2) and have very good accuracy.
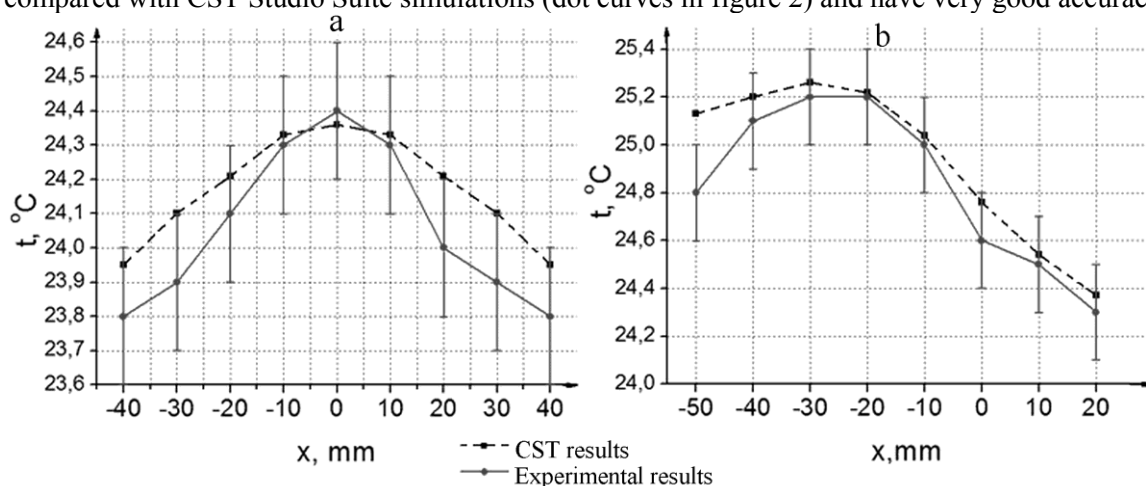

Figure 2. Temperature distributions after heating for in-phase dipoles on (a) and for 60 degrees phase shift (b).

5. Conclusions

The system for local hyperthermia of deep seated tumours which is planning to use further for combined cancer thermoradiotherapy is presented. It was shown by means of electrodynamics and thermal simulations that system of a number of independently phased dipoles is suitable for local heating of deep suited tissues. The first experimental prototype was constructed and numbers of heating localization experiments were carried out. Comparison of simulation and experiments shows that the phased array solve the local heating problem and deep suited tumorous can be locally heated and treated.

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