Thermometry system development for thermoradiotherapy of deep-seated tumours

A M Fadeev¹, S M Ivanov¹², E A Perelstein³, and S M Polozov¹

¹National Research Nuclear University - Moscow Engineering Physics Institute, Moscow 115409, Russia
¹¹N.N. Blokhin Russian Cancer Research Center, Moscow 114478, Russia
³Joint Institute for Nuclear Research, Dubna 141980, Russia
SMPolozov@mephi.ru

Abstract. Therapeutic hyperthermia (including RF hyperthermia) in combination with radiotherapy (called thermoradiotherapy) is one of widely used contemporary cancer treatment methods. The independent electron linac and RF system or their combinations are necessary for effective therapy. Whole-body hyperthermia is used for treatment of metastatic cancer that was spread throughout the body, regional one is used for treatment of part of the body (for instance leg or abdominal cavity). Local hyperthermia with characteristic size of heating volume of 20-100 mm permits to heat tumour without overheating of healthy tissues. The thermometry of deep suited tissues during the hyperthermia process is an important and complex task. Invasive methods as thermistors, optical sensors or thermo-couples can not be widely used because all of them are able to transport tumor cells to the healthy region of the patient body. Distant methods of the temperature measurement such, as radiothermometry and acoustic thermometry can not be used for tissues seated deeper than 5-7 cm. One of possible ways to solve the problem of temperature measurement of the deep suited tissues is discussed in this article: it was proposed to use the same electrodes for RF hyperthermia and thermometry. As known electrodynamics characteristics of tissues are sufficiently depends on temperature. It was proposed to use this effect for active radiothermometry in local hyperthermia. Two opposite RF dipoles can be used as generator and receiver of pick-up signal.

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. The thermal therapy combined with the radiation (thermoradiotherapy, TRT) has been applied in N.N. Blokhin Russian Cancer Research Center (RCRC) since 1980th [1]. 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). For instance, 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 from 395) for surgery and 9.6±2.1% (26 from 272) for surgery and before radiotherapy [1]. 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. [2].
RCRC clinical studies demonstrate improving results of treatment by combined using of hyperthermia and radiation for the several tumour localizations. But only applicators for superficial hyperthermia were used in RCRC. Common RCRC-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 diseases treatment [2-7]. The most evident approach is using an annular array of applicator situated around the patient body [8]. Arrays of applicators with variations in frequency, phase, amplitude and orientation in space give more possibilities to control heating pattern during hyperthermia treatment [3]. Top view of this structure is shown in the figure 1. 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 variation of phases $\Phi_i$ and amplitudes $A_i$ of each dipole provides to control the heating volume size and localization (see figure 1). The operating frequency choice is also important because the higher frequency allows to decrease the heating volume. As an example modeling of head and neck hyperthermia with operating frequency of 433 MHz produces heated area size of 15-20 mm comparatively with 30-40 mm with 150 MHz antennae array.

The RF power feeding scheme of the designed local hyperthermia facility is presented in figure 2 and discussed in [4]. The operating principle of such layout is the following. The RF signal at an operating frequency from signal source splits into eight channels. Then by means of controlled eight phase shifters and eight solid state amplifiers we can adjust phase and amplitude of every signal. Due to these adjustments electric field is focused indesirable region. Directional couplers prevent reaching reflected wave to generator. Reflected wave will be absorbed by 50 Ohm load.

The first experimental prototype was constructed at MEPhI and numbers of heating localization experiments were carried out [7, 9]. Comparison of simulation and experiments shows that the phased array solve the local heating problem and deep suited tumorous can be locally heated. Experimental heating results are compared with CST Studio Suite simulations and have very good accuracy.

2. Problem of the thermometry for deep seated tissues

It is clear, RF hyperthermia is a way to increase the efficiency of the combined cancer therapy. But the problem of the temperature control inside of the patient body especially for heating tissues should be solved before routine clinical usage of the local RF hyperthermia. Thermometry is more difficult for deep-seated tissues. It is possible to use invasive or contact thermometry systems as thermistors and thermo-couples for deep-seated tissues and tumours. Optical fiber sensors based on Bregg’s grids became more popular last years. The measured parameter as temperature or mechanical displacement is converted to the length of the light shift. But all of such sensors provide only invasive temperature measurement. Russian hyperthermia protocol permits installation of thermocouples inside the patient body. But this causes pain and temperature probe can transport tumor cells to the healthy region of the patient body. European hyperthermia protocol directly forbids the installation of any temperature probes inside the patient body. They prefer to simulate any radiation process with phantoms. Moreover noninvasive thermometry of human tissues is important for other cases. It is suggested to determine tissues temperature by means of measurements effects that could be observed during heating. Noninvasive control is possible by using of the magnetic resonance imaging (MRI) as it is proposed and realized by BSD Medical Systems (now Pyrexar Medical). But such way has serious difficulties and the price of MRI system is higher than the same of the hyperthermia system. Acoustic thermometry is one of new technologies. 2D and 3D temperature distributions were successfully imaged by means of acoustic thermometry experiments. But such technique can be used only for tissues located not deeper than 3-5 cm (for mammography as an example). Well-known radiothermometry (RTM) also can be used for deep-seated tissues. As known, the specific heat of tumour is directly proportional to its growth velocity. The faster growing tumours will be “hotter” and
will be brighter on the thermograph. The possibility to find the fast growing tumours is an unique advantage of the RTM. Main sufficient disadvantage is inherent as for acoustic thermometry: RTM can not be used for the deep suited tissues. The depth of temperature anomaly localization will not be greater than 3-7 cm depending of the tissues humidity.

**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.

**Figure 2.** RF power system of the hyperthermia facility schematic layout, here 1 – master generator with input signal’s frequency range 100 – 400 MHz and input impedance 50 Ohm; 2 – 8-out power splitter; 3 – voltage-controlled phase with phase range 180°; 4 - solid state amplifier with output power up to 100 W, 5 – 10 dB unidirectional coupler 6 – load absorbed, 50 Ohms, 7 – phased array with patient body inside.

3. **Active radiothermometry with RF hyperthermia dipoles**

As known dielectric properties of the tissues (complex dielectric permittivity and tangent of the dielectric loss) depend of temperature. It is suggested to determine tissues temperature by means of measurements effects that could be observed during heating process. Thus dielectric properties of the human tissues sufficiently varies with temperature increasing (fat tissue and skin are not heated during hyperthermia with the phased array). This thermometry system could be used as addition to the other regional or local hyperthermia facilities.
The detail study of dielectric properties of the human body tissues was done in [10-12]. Let us discuss the main equations which can be used to determine the temperature and the frequency dependences of the complex dielectric permittivity of tissues. It can be described using the Debye expression

\[ \hat{\varepsilon}(\omega) = \varepsilon_\infty + \sum_{k=1}^{5} \frac{\Delta \varepsilon_k}{1 + j\omega\tau_k} + \frac{\sigma_i}{j\omega\varepsilon_0}. \]  

(1)

where \( \varepsilon_\infty \) is the permittivity at \( \omega \tau >> 1 \) and \( \varepsilon_\infty \) is the same value for \( \omega \tau << 1 \), \( \omega \) is the operating angular frequency, \( \tau \) is the relaxation time. The magnitude of the dispersion is equal \( \Delta \varepsilon = \varepsilon_s - \varepsilon_\infty \). The other way was proposed by Hurt for muscle tissue model [13] were dispersion present as a set of approximating coefficients and taking into account the static ionic conductivity of tissues \( \sigma_i \):

\[ \hat{\varepsilon}(\omega) = \varepsilon_\infty + \sum_{k=1}^{5} \frac{\Delta \varepsilon_k}{1 + j\omega\tau_k} + \frac{\sigma_i}{j\omega\varepsilon_0}. \]  

(2)

Here \( \varepsilon_\infty \) is the permittivity of the free space. The modification of the Debye equation is known as Cole-Cole model:

\[ \hat{\varepsilon}(\omega) = \varepsilon_\infty + \frac{\Delta \varepsilon}{1 + (j\omega\tau)^{1-\alpha}}. \]  

(3)

where the distribution parameter \( \alpha \) is a measure of the dispersion broad. The Hurt and the Cole-Cole models can be generalized due to:

\[ \hat{\varepsilon}(\omega) = \varepsilon_\infty + \sum_{k=1}^{5} \frac{\Delta \varepsilon_k}{1 + (j\omega\tau_k)^{(1-\alpha)}} + \frac{\sigma_i}{j\omega\varepsilon_0}. \]  

(4)

The values of \( \Delta \varepsilon_k, \sigma_i, \tau_k \) and \( \alpha_k \) for different tissues and for the frequency band above 400 MHz can be founded in [12]. As an example, the real part of dielectric permittivity of the muscle tissue or tumour tissue grows by 0.2-0.5 per 1 degree (absolute value is 70-100). It leads to the special absorption rate variation and to RF power scattering modification in tissues. Such variation can be registered. A number of examples of real \( \varepsilon' \) and imaginary \( \varepsilon'' \) components of the complex dielectrical permittivity \( \varepsilon = \varepsilon' - j\varepsilon'' \) are shown in figure 3. Dependences are modelled for tissues using data from [10-12]. The operating frequency is 150 MHz. It is clear that such dependences are close to linear for temperature range 36-43°C which is used for thermoradiotherapy. The analyses of experimental and simulated data form [10-12] shows that for operating frequency of 150 MHz absolute values of \( \varepsilon' \) and \( \varepsilon'' \) are close for all tissues. Only dielectric properties of fat tissues differ very significantly.

Each dipole antennae feeds independently in the hyperthermia facility proposed in [2-7]. Each feeding channel includes RF circulator (see figure 4) to prevent the back wave penetration to the other feeding channels. Such system with minor modifications can be also used for thermometry. In the temperature measurement regime two feeding channels (RF input #1 and #5 in figure 4) will be switched to low RF power regime and the feeding of all other dipoles will be turned off. The output of the circulator directs the transmitted back wave to the band-pass filter and further to the measuring PIN-diode. PIN-diode measures the time dependence of the RF power flux for further A/D conversion. Digital signal processes by the especially developed Fourier analyses code and time dependences of Fourier coefficients define. Current spectral series compares with “non-perturbed” signal which was previously defined for not heated patient body. Proposed radiothermometry technique differs very sufficiently from the conventional one: the thermometry system is combined with hyperthermia one and dipole antennae are used both for heating and thermometry; the thermometry can be realized for deep situated tumours and tissues; the noninvasive thermometry can be realized and the active tissues scanning can be used for the 2D temperature imaging.
Figure 3. Dependences of real $\varepsilon'$ and imaginary $\varepsilon''$ components of the complex dialectical permittivity for muscle tissue (red), liver (blue), kidney (green), spleen (brown), not infiltrated fat (black) and dry skin (cyan). The operating frequency is 150 MHz.

Figure 4. The scheme for measurement and analysis of the transmitted signal.

The CST simulation of the heating process with temperature control was done to verify the proposed thermometry technique. The fast Fourier analysis by the especially designed code was done to define the spectral distribution of the transmitted signal as the function of temperature. The main signal harmonic amplitude was controlled and the temperature distribution and its time dependence were calculated. The TRT facility was developed to heat only limited volume inside the patient’s body. Only characteristics of such local area will influence to the transmitted signal. Its harmonic distribution and temperature control will be also provided for local volume where heating is taking place. Numerical simulations show that the amplitude of the main Fourier harmonic of the transmitted signal depends on the temperature linearly. The simulation model is shown in [6], it includes voxel model of the human body with a number of tissues and organs. The dielectric characteristics of tissues were varied during simulation with the temperature increases. The detected transmitted signal is shown in figure 5. Such detected signal expands to the Fourier series and its coefficients are compared with the “base” distribution which was done and safe for non-perturbed (not heated, $T=37 ^\circ C$) model. It is clear from Figure 5 that the main signal harmonic amplitude depends vs. temperature linearly. Such result simplifies the back problem of the temperature reconstruction for heated volume. About 90 % of RF power absorbs by patient body during local or regional hyperthermia as it was shown by numerical simulation. The RF power necessary for effective treatment is up to 100 W/dipole for facility proposed in [2-7]. The simulation of the heating process with temperature control shows that for the first Fourier harmonic of the transmitted signal the variation is about $\sim 10^{-3}$ form coefficient value for the local hyperthermia and $\sim 10^{-2}$ for the regional one. Temperature increasing range is about 37-43°C. It is clear that the transmitted power measurement accuracy should be better than 100 $\mu$W (for measurement signal power is $\sim$1 W). The accuracy of the temperature measurement for the local heated volume will be better than 0.3°C due to such RF power accuracy measurement. Such result is better than for conventional radiothermometry and close to tolerance for invasive thermo-couples or thermistors. The process of local thermoradiotherapy takes 15-30 minutes usually and it is quite enough to measure the temperature 1-3 times/minute.


Figure 5. Temperature dependence of the difference (a.u.) of transmitted signal amplitudes for current and “base” (T=37°C) temperatures into the heated volume (top) and the temperature dependence of the first Fourier harmonic amplitude.

4. Conclusions
It was shown that dipole antennae of the TRT facility can be used both for heating and for temperature measurement and active radiothermometry of the deep-seated tumours can be realized. The accuracy of the thermometry for the local heated volume is better than 0.3°C with low (~1 W) measuring signal value. This project is supported in part by the MEPhI 5/100 Program of the Russian Academic Excellence Project.

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