EFFECT OF MICROWAVE HYPERTHERMIA ON TUMOR TREATMENT

RASHA SAID SHAMS ELDINE, M.M. MOHAMED**, M.B. TAYEL***, H. ALI NOUR****

*Medical Biophysics Department, Medical Research Institute, Alexandria University,
E-mail: rasha_shams17@yahoo.com
**Faculty of Science, Pharos University
***Faculty of Engineering, Alexandria University

Abstract. Cancer treatment is one of main challenges that face the scientific centers all over the world. The cancer incidence percentage increases year after year. Hyperthermia elevated tissue temperature by radio frequency (RF) and microwave fields have beneficial effects in cancer therapy. Particularly, in noninvasive electromagnetic (EM) hyperthermia, one attempts to focus the energy in the tumor region, while avoiding damage to the surrounding healthy tissue. The present work is concentrated on the use of horn antenna as a noninvasive hyperthermia applicator. Animals with Ehrlich tumor were divided into two main groups (intramuscularly and subcutaneous) and has been exposed using this horn antenna at microwave of 2450 MHz and 40 W or 50 W for 8 min. Tumor growth was examined regularly every 2 days, the measurements of the dielectric properties of the solid tumor were done after killing the animals. The real permittivity for both the exposed groups either intramuscular or subcutaneous decreased with increasing the applied frequency while the conductivity increased with increasing the applied frequency. The effect of the microwave therapy increases with increasing of its energy for both the exposed groups in comparison to the non-exposed group.

Key words: Cancer treatment, microwave hyperthermia, dielectric properties.

INTRODUCTION

Microwave hyperthermia is a non-ionizing form of radiation therapy that can substantially improve results for cancer treatment. Tumors cells are considered to be more susceptible to hyperthermia effects than healthy cells because of higher metabolic rate [1, 9, 21]. Hyperthermia has been proven to increase the response of malignant tumors to radiation therapy in both experimental animal tumors and the clinical treatment of human cancer [8]. This treatment is toxic for the tumor itself, making the tumor more sensitive to traditional chemo- and radiation therapies. This in turn leads to reducing treatment side effects by reducing radiation doses and cytostatic drugs with unchanged treatment results.

Received July 2013;
in final form December 2013.

ROMANIAN J. BIOPHYS., Vol. 23, No. 4, P. 249–259, BUCHAREST, 2013

Localized hyperthermia has particular relevance in the treatment of primary tumors and early stage cancers. Numerous studies have demonstrated marked reduction in tumor size after treatment by localized hyperthermia [3, 5, 10, 22].

The dielectric properties of biological cells and tissues are very remarkable. They typically display extremely high dielectric constants at low frequencies, falling off in the more or less distinct steps as the applied frequency is increased. Their frequency dependence permits identification and investigation of a number of completely different underlying mechanisms, and hence dielectric studies of biomaterials have long been important in electrophysiology and biophysics. The dielectric behavior of biological tissues depends ultimately on the properties of the molecules comprising it. Consequently, interpretation of the dielectric information can therefore provide us with useful information on the molecular level [6].

This work aimed to study the effects of microwave induced hyperthermia on the biophysical properties Ehrlich tumors injected in mice. An antenna with minimum set up of complexity with the whole system was designed. The dielectric properties of tumors have been measured to reveal the microwave exposure effect.

MATERIALS AND METHODS

EXPERIMENTAL ANIMALS

A total of 60 female Swiss albino mice, 4 weeks old, of mean weight 25 g were purchased from Medical Research Institute, Alexandria University, Egypt. Groups of 10 animals were housed in cages in a well ventilated room with diet and water. Approximately 2×10^6 Ehrlich ascites carcinoma cells, mammary in origin, have been suspended in an appropriate volume of 0.9% saline and injected intramuscularly to a group of 30 mice. Other groups of 30 mice were injected subcutaneously. A week later, the tumor reached a size of about 0.5–1 cm in diameter.

Tumor bearing mice were divided into six groups:

1. Group (1) 10 mice injected subcutaneously served as control.
2. Group (2) 10 mice injected intramuscularly served as control.
3. Group (3) 10 mice injected subcutaneously and treated with microwave at a power of 40 W for 8 min.
4. Group (4) 10 mice injected intramuscularly and treated with microwave at a power of 40 W for 8 min.
5. Group (5) 10 mice injected subcutaneously and treated with microwave at a power of 50 W for 8 min.
6. Group (6) 10 mice injected intramuscularly and treated with microwave at a power of 50 W for 8 min.

At the end of microwave exposure period, Ehrlich tumor tissues were taken from all groups of mice, and the dielectric measurements have been done on each tumor excised from each animal.

MICROWAVE UNITS

The main thrust of this work is to optimize the non-invasive microwave antenna for locally-induced hyperthermia for cancer therapy. The horn antenna was chosen for the following reasons:

- Easy to design.
- Minimum set up complexity with the whole system.
- Lightweight-to increase comfort and mobility during treatment.
- Low cost.

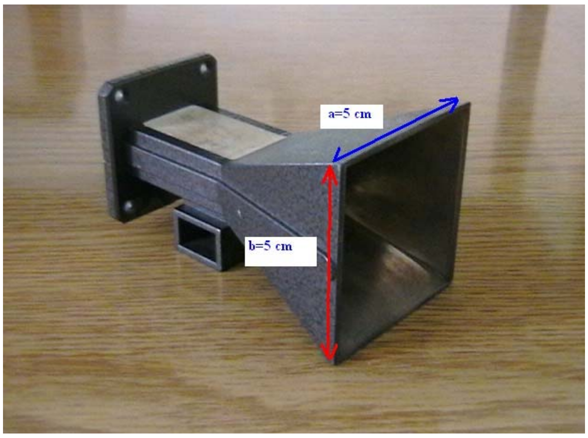

Fig. 1. RF antenna.

The microwave generator used in the present work. All complete microwave generator systems are supplied with a power supply magnetron head, cable assembly and isolator. Richardson Electronics offers design and production services to build custom turnkey microwave generators for both low and high power applications in the standard frequencies of 2450 MHz and power 150 W.

DIELECTRIC MEASUREMENTS

At the end of exposure period, dielectric measurements were made on the tumors excised from the all groups of animals. A RCL meter (Resistance (*R*), Capacitance (*C*), and Inductance (*L*)) Fluke PM6306 Programmable Automatic RCL Meter has been used in this study.

In order to perform measurements on tumor cells using RCL meter an electric cell was designed for this purpose. The tumor samples were connected to RCL meter by means of two parallel locally electrodes mounted in a measuring cell (Fig. 2). The samples were inserted between two circular gold electrodes with a radius of 3.055 mm each. The distance between the electrodes was 0.5 cm. The tumor specimens were inserted between the electrodes in a close contact with them. The electrodes were held in position during measurements by means of gallows like stand. The gallows stabs were used only for convenience in supporting the movable electrodes.

The *R* and *C* have been recorded for frequency ranging between 100 Hz and 1 MHz.

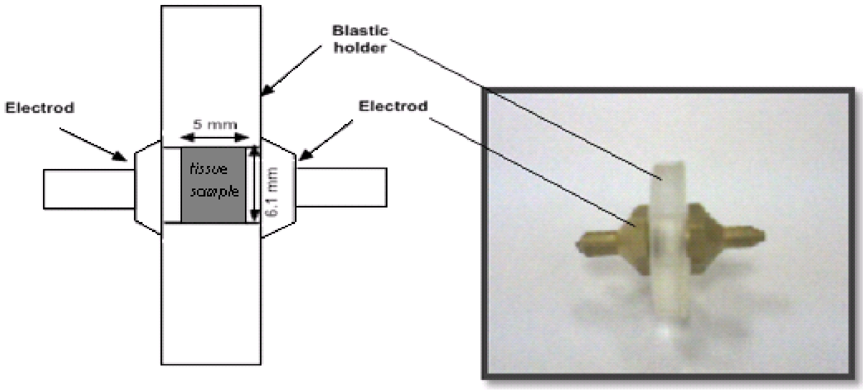

Fig. 2. The constructed dielectric cell.

The measured values of capacitance (*C*) and conductance ($G = 1/R$) were used to calculate the sample conductivity (σ), real *ε'* and imaginary parts *ε"* of the complex permittivity, using the following equations:

$$\sigma = \frac{d}{A} G \qquad (1)$$

$$\varepsilon' = \varepsilon_r = \frac{d}{A}\frac{C}{\varepsilon_0} \qquad (2)$$

$$\varepsilon'' = \left(\sigma - \sigma_L\right) / 2\pi f \varepsilon_0 \qquad (3)$$

where: ε_0 is the permittivity of free space (8.85×10^{-12} F/m); *d* and *A* are the average separation between the electrodes and the surface area of electrodes (approximately the thickness length and cross-sectional area of the sample); σ_L is the conductivity at low frequency; *f* is the applied frequency.

The recordings on the frequency range have been done on each excised tumor and mean values (± SD) of the parameters have been calculated for each group of animals (10–20) and plotted against the frequency.

RESULTS

The dielectric parameters of the tumor samples (conductivity, permittivity real and imaginary parts) were determined by applying electric field from 100 Hz up to 1 MHz while recording the variation of both capacitance and resistance.

In Figure 3 the frequency dependence of measured conductivity of the intramuscular inoculated tumors, for control and for the microwave treated samples (either 40 W or 50 W) has been plotted against frequency. Similarly, Figure 4 shows the frequency dependence of measured conductivity of the subcutaneous inoculated sample (control and the treated with microwave at 40 W or 50 W).

Generally, with increasing frequency the conductivity increases in all measured samples. Moreover, the microwave exposed groups show higher values of conductivity than the control over all the frequency range.

The relation between the real permittivity of samples and the frequency is shown in Figure 5 for the intramuscular inoculated tumors (both control and treated with microwave at 40 W or 50 W), while Figure 6 shows a similar plot for the subcutaneous inoculated tumors.

Figure 7 shows the frequency dependence of imaginary part of the samples permittivity of the intramuscular inoculated tumors (both control and exposed to microwave at 40 W or 50 W), while Figure 8 shows the similar dependence of the subcutaneous inoculated tumors.

For all the measured samples both the real and imaginary permittivities decrease with the increasing in frequency over all the frequency range. On the other hand, the microwave exposed tumors show higher values for these parameters comparing with the control (higher the microwaves power higher the permittivity values).

DISCUSSION

Hyperthermia is one of the most promising new multidisciplinary approaches to cancer therapy [11]. Cancer cells exhibit both lower electrical membrane potentials and lower electrical impedance than normal cells. Since injured and cancerous cells cannot maintain a normal membrane potential they will have electronic dysfunctions that will impede repair and the reestablishment of normal metabolic functions. Therefore a key component of cell repair and cancer treatment would be to reestablish a healthy membrane potential in the body’s cells [9].

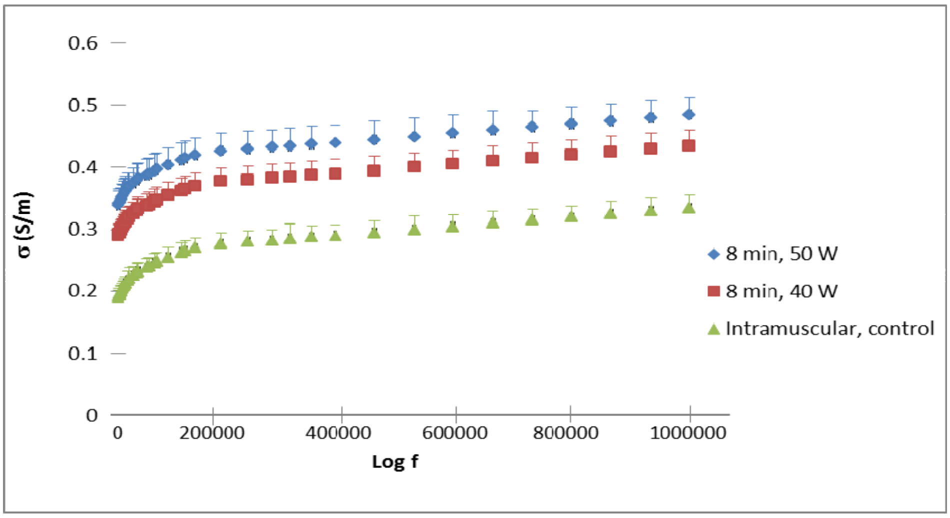

Fig. 3. The electric conductivity of intramuscular sample exposed to microwave as a function of frequency.

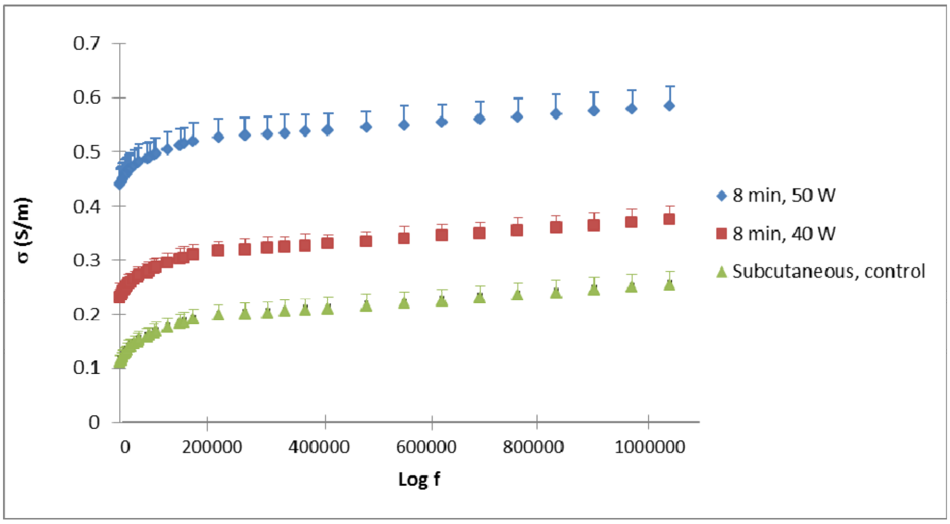

Fig. 4. The electric conductivity of subcutaneous sample exposed to microwave as a function of frequency.

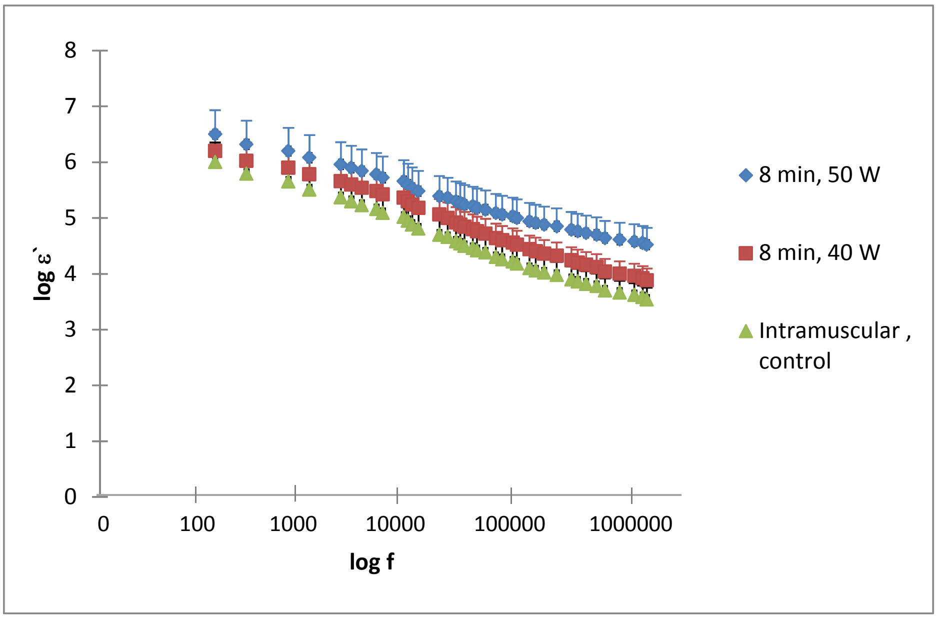

Fig. 5. The log of real permittivity of intramuscular sample exposed to microwave as a function of frequency.

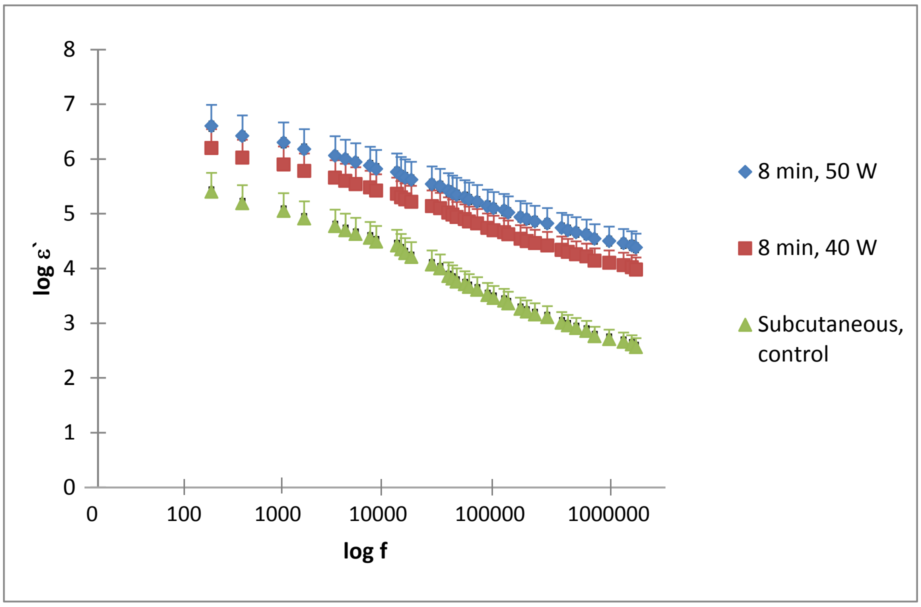

Fig. 6. The log of real permittivity of subcutaneous sample exposed to microwave as a function of frequency.

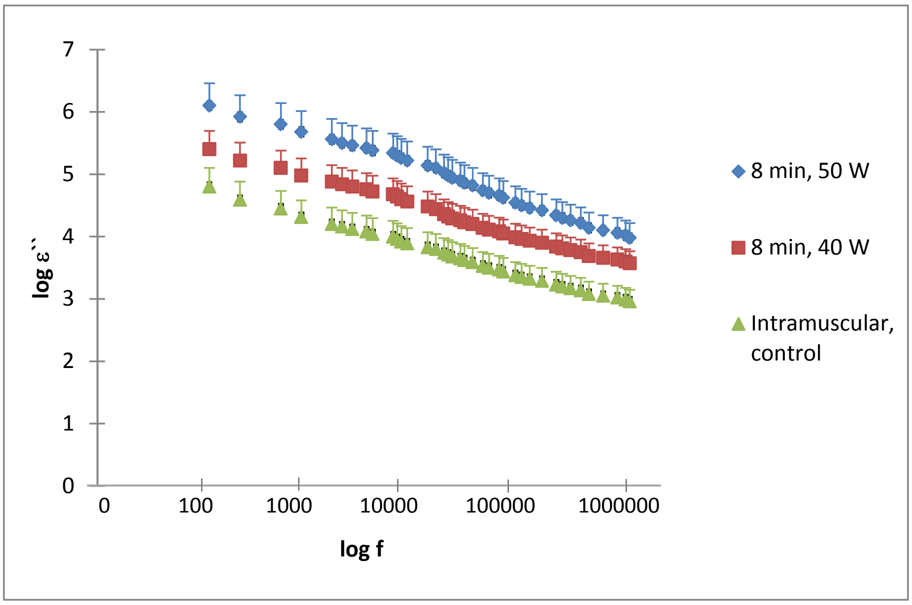

Fig. 7. The log of imaginary permittivity of intramuscular sample exposed to microwave.

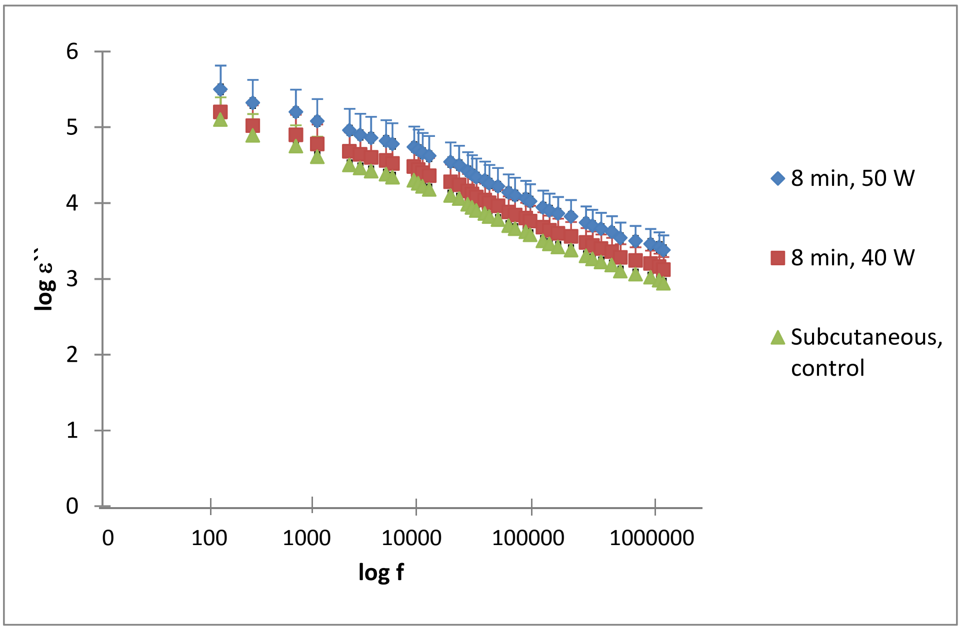

Fig. 8. The log of imaginary permittivity of subcutaneous sample exposed to microwave.

Benign and malignant tumors may be determined from the differences in the electrical properties of such tissues [2]. It has been reported that there are measurable differences between the electrical impedances of normal breast tissue, benign breast tumors, and malignant breast tumors [9].

Permittivity is a physical quantity that describes how an electric field affects and is affected by a dielectric medium. It is determined by the ability of a material to polarize in response to the field, and thereby reduces the total electric field inside the material. Thus, permittivity relates to a material's ability to transmit (or "permit") an electric field [20]. Particularly, in the case of biological tissues, the ions displacement, molecules reorientation and polarization in different compartments of the cells (plasma membrane, cytosol) explain the high values of real permittivity at low frequency and the decrease of this parameter (accompanied by the increase of conductivity) at higher frequencies. In the low frequency range used in our measurements (100 Hz – 1 MHz) the interfacial polarization at the level of plasma membrane surfaces is the main polarization mechanism. In this context, an increase of real permittivity with the exposure to microwaves suggests a higher capacity of membrane to accumulate ions on the surfaces, proving a clear change induced by microwaves in this cellular compartment.

The results reported in this paper are in agreement with other studies done in this field where it shows that cancerous cells demonstrate greater permittivity [9], which reflects the ability to resist the formation of an electrical field and to resonate differently from normal cells.

The dielectric dispersion can be correlated to change in both cell membrane and extracellular matrix state after treatment [18]. Indeed, the variation of conductivity and permittivity with frequency in case of using microwave exposure (40 W and 50 W) on intramuscular and subcutaneous tumors revealed that all exposed samples have higher conductivity and permittivity than those of non exposed groups. This might be associated with the fact that tumor cells have a high amount of water content and sodium concentration, as well as different electrochemical properties of their cell membranes [4, 6, 7, 12, 13, 14, 15, 17, 19, 20].

Thus, our findings suggest that some characteristics of the electrical impedance of tumor tissue can be explained by changes at the cellular level. This relation opens the way to assessment of tissue structure from electrical impedance spectral measurements. For example, measurements might be important for screening of the precancerous changes.

CONCLUSIONS

Our findings prove a clear change of microwave exposed tumors electrical impedance. The changes are correlated with the microwaves power, suggesting that the microwave frequency of 2450 MHz could be a useful tool in the treatment of tumors by hyperthermia.

REFERENCES

1. CAMPBELL, A.M., D.V. LAND, Dielectric properties of female human breast tissue measured in vitro at 3.2 GHz, *Phys. Med. Biol*., 1992, **37**(1), 193–210.
2. DEWHIRST, M.W., F.A. GIBBS, R.B. ROEMER, T.V. SAMULSKI, Hyperthermia, in *Clinical Radiation Oncology*, L.L. GUNDERSON, J.E. TEPPER eds., Churchill Livingstone Inc., 1999, pp. 43–53.
3. DEWHIRST, M.W., P.K. SNEED, Those in gene therapy should pay closer attention to lessons from hyperthermia, *Int. J. Rad. Oncol. Biol. Phys*., 2003, **57**, 597–600.
4. EGGERS, P.E., A. SHMULEWITZ, *Apparatus and Method for Characterization and Treatment of Tumors*, United State Patent: 5,928,159, 1999.
5. FALK, M.H., R.D. ISSELS, Hyperthermia in oncology, *Int. J. Hyperthermia*, 2001, **17**(1), 1–18.
6. HAMAZAOE, R., Y. HIROOKA, S. OHATANI, T. KATOE, N. KABARA, Intraoperative microwave tissue coagulation as treatment for patients with nonresectable hepatocellular carcinoma, *Cancer*, 1995, **75**, 794–800.
7. HAND, J., D. MACHIN, C. VERNON, J. WHALEY, Analysis of thermal parameters obtained during phase III trials of hyperthermia as an adjunct to radiotherapy in the treatment of breast carcinoma, *Int. J. Hyperthermia*, 1997, **13**, 343–364.
8. HYNYNEN, K., A. CHUNG, T. FJIELD, M. BUCHANAN, D. DAUM, V. COLUCCI, P. LOPATH, F. JOLESZ, Feasibility of using ultrasound phased arrays for MRI monitored noninvasive surgery, *IEEE Trans. Ultrasonic*, 1996, **43**, 1043–1053.
9. JOINES, W.T., Y. ZHANG, C. LI, R.L. JIRTLE, The measured electrical properties of normal and malignant human tissues from 50 to 900 MHz, *Med. Phys*., 1994, **21**(4), 547–550.
10. KAPP, D.S., G.M. HAHN, R.W. CARLSON, Principles of hyperthermia, in: *Holland-Frei Cancer Medicine*, 5th ed., R.C BAST JR., D.W. KUFE, R.E. POLLOCK, R.R. WEICHSELBAUM, J.F. HOLLAND, E. FREI, Hamilton, Ontario, B.C. Decker Inc., 2000, chapter 35.
11. LEOPOLD, K, M. DEWHIRST, T. SMALSKI, Relation among tumor temperature, treatment time and histopathological outcome using preoperative hyperthermia with radiation in soft tissue sarcomas, *Int. J. Rad. Oncol*., 1992, **23**, 989–998.
12. MOROS, E.G., X. FAN, W.L. STRAUBE, Experimental assessment of power and temperature penetration depth control with a dual frequency ultrasonic system, *J. Med. Phys*., 1999, **26**, 810–817.
13. MYERSON, R.J., E. MOROS, J.L. ROTIROTI, Hyperthermia, in: *Principles and Practice of Radiation Oncology*, 3rd ed., C.A. PEREZ, L.W. BRADY eds., Lippincott-Raven, Philadelphia, 1998, pp. 637–683.
14. MYERSON, R.J., W.L. STRAUBE, E.G. MOROS, B.N. EMAMI, H.K. LEE, C.A. PEREZ, M.E. TAYLOR, Simultaneous superficial hyperthermia and external radiotherapy: report of thermal dosimetry and tolerance to treatment, *Int. J. Hyperthermia*, 1999, **15**, 251–266.
15. NOVAK, P., E.G. MOROS, W.L. STRAUBE, R.J. MYERSON, SURLAS: a new clinical grade ultrasound system for sequential or concomitant thermoradiotherapy of superficial tumors: applicator description, *J. Med. Phys*., 2005, **32**, 230–240.
16. OSINSKY, S., V. PROTSYK, Twenty years experience in local microwave hyperthermia combined with radio- and/or chemotherapy in Ukraine, *22nd Conference International Clinical Hyperthermia Society*, Poltava, Ukraine, 2–4 April, 1999.
17. SAMULSKI, T.V., W.J. GRANT, J.R. OLESON, K.A. LEOPOLD, M.W. DEWHIRST, P. VALLARIO, J. BLIVIN, Clinical experience with a multi-element ultrasonic hyperthermia system: Analysis of treatment temperatures, *Int. J. Hyperthermia*, 1990, **6**, 909–922.
18. SCHARFETTER, H., Structural Modeling for Impedance-Based Non-Invasive Diagnostic Methods, Thesis for the habilitation at the Faculty of Electrical Engineering, Technical University Graz, 1999.

19. STAUFFER, P., F. ROSSETTO, M. LEONCINI, G. GENTILLI, Radiation patterns of dual concentric conductor micro strip antennas for superficial hyperthermia, *IEEE Trans. Biomed. Eng*., 1998, **45**, 605–613.
20. UNDERWOOD, H.R., E.C. BURDETTE, K.B. OCHELTRE, R.L. MAGIN, A multielement ultrasonic hyperthermia applicator with independent element control, *Int. J. Hyperthermia*, 1987, **3**, 257–267.
21. VARGAS, H.I., W.C. DOOLEY, A.J. FENN, Study of preoperative focused microwave phased array thermotherapy in combination with neoadjuvant anthracycline-based chemotherapy for large breast carcinomas, *Cancer Ther.,* 2007, **5**, 401–408.
22. WUST, P., B. HILDEBRANDT, G. SREENIVASA, B. RAU, J. GELLERMANN, H. RIESS, R. FELIX, P.M. SCHLAG, Hyperthermia in combined treatment of cancer, *Lancet Oncol*., 2002, **3**(8), 487–497.