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Microwave Thermotherapy and Its Clinical Applications

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Abstract

In this paper, a review of the use of microwave energy for thermotherapy (hyperthermia/ablation therapy is reported. The advantages of hyperthermia/ablation therapy over radio- and chemo-therapies, and the techniques for estimation of specific absorption rate (SAR) are discussed. The review includes its history, description of various types of applicators and temperature sensors developed for hyperthermia/ablation therapy, and clinical applications of hyperthermia/ablation therapy. In addition, Oncothermia, which is a method of hyperthermia for oncological use is also introduced.

1. Introduction

Conventional methods used for cancer treatment are radiotherapy and chemotherapy. These therapies have certain disadvantages, which include ionization property of radiotherapy and side effects of chemotherapy. Another form of cancer therapy is called thermotherapy in which temperature of the cancerous region is raised above the normal body temperature. Thermotherapy involves using hot water, radio waves, microwaves, ultrasound waves and lasers to heat the affected cancerous region. Thermotherapy can be divided into three categories according to the target temperature level/interval: diathermy – raising the temperature upto 41^0C, hyperthermia – raising the temperature in the interval 41-45^0C and thermoablation – raising the temperature above 45^0C. The term 'hyperthermia' is a combination of two Greek words: hyper (raise) and therme (heat) and refers to the elevation of body temperature or temperature of selected tissues in order to achieve a specific therapeutic effect. Systemic (excluding head and heart) hyperthermia therapy (Steam therapy), a part of clinical protocol 'Panchakarma' in Ayurveda began in India more than 3000 years ago for detoxification of the body. Hippocrates (460-375 BC), a Greek philosopher and scientist successfully used heat therapy to treat breast tumors. French physician, physiologist and physicist, A. d'Arsonval (1851-1940) is called the father of electromagnetic heating. He invented long wave diathermy through inductive and capacitive heating of human beings and animals using a frequency of 500 kHz. In 1866, German surgeon Carl D. W. Busch published the first paper on hyperthermia in which he described the removal of advanced sarcoma tumor on the face of a 43 year old woman due to fever caused by erysipelas. Interested researchers may go through the references [1, 2] for details of the history on hyperthermia.

The use of 25-30 cm microwaves for therapeutic purposes was proposed by Hollman of Germany in 1938-39. He predicted that the waves could be focused to produce heating of deep tissues without excessive heating of the skin. Similar predictions were made by Hemingway and Stenstrom in in the United States in 1939. Before World War II, due to lack of the availability of microwave sources, diathermy continued to be applied at frequencies below 100 MHz. In June 1946, Raytheon Company supplied 3 GHz magnetron tube to the Mayo Clinic for medical research. With this equipment, therapeutic application of microwaves began at the Mayo Clinic in 1946. This application involved exposure of laboratory animals to 3 GHz fields at an output power of 65 W. After this, a lot of work has been done to improve the performance of hyperthermia applicators for treatment of cancer. For details of work done on microwave hyperthermia upto early 1980s, interested researchers can go through the papers listed in references [1-3]. Some important sources of information for the work done on the subject during the period since early 1980's can be found in the literature [4-14] as well as in the January 1984 issue of IEEE Transactions on Biomedical Engineering, May 1986, October 1996 (Part 2) and August 2004 (Part 2) issues of the IEEE Transactions on Microwave Theory and Techniques, and different issues of the International Journal of Hyperthermia, the official journal of the Society for Thermal Medicine, the European Society for Hyperthermic Oncology and the Japanese Society for Thermal Medicine and published by Taylor and Francis.
Microwaves have been used for heating the cancerous tissues because these waves can easily be focused within the tumor volume with the help of relatively smaller size antennas as compared with RF waves. Following factors indicate that microwave hyperthermia increases the sensitivity of cancer cells to radiotherapy and chemotherapy: i) Some of the cancerous cells are hypoxic and hypoxic cells are resistant to X-radiation, ii) The deficiency of blood supply in tumor region aids in heat accumulation, iii) Further, tumor cells are found to contain higher levels of water and ionic contents and therefore these cells have higher conductivity as

compared to normal cells which enhances EM energy absorption and iv) hyperthermia coupled with chemotherapy has been found to be effective in the treatment of bladder cancer. Initiation of worldwide interest in hyperthermia was aroused by organizing first international symposium on cancer therapy by hyperthermia and radiation in Washington, D.C. (USA) in 1975. Other similar congresses took place in Essen (Germany) in 1977, and in Fort Collins (Colorado, USA) in 1980. Since then, the International Symposium on Hyperthermic Oncology has been held every four years. More recent concept related to hyperthermia is oncothermia, which is a method of hyperthermia for oncological use, controlling the locally applied deep heat by selectively targeting the cellular membrane of the malignant cells. The selection of the method is based on various biophysical and biochemical phenomena. The first International Oncothermia Symposium was held in Cologne, Germany in 2010.

The treatment can be called local, regional/deep tissue or whole body hyperthermia, depending upon the size and depth of the tumor. Further, ISM frequencies of 433.92 MHz, 915 MHz, and 2.45 GHz are usually employed for microwave hyperthermia and ablation therapies.

In this paper, a review of hyperthermia/ablation therapy employing microwave energy is presented. The mechanisms for generation of heat using microwave energy and killing of tumor cells using microwave hyperthermia/ablation therapy are discussed. Further, a review of various techniques used for estimation of power absorbed per unit mass of the tissue i.e. specific absorption rate (SAR) as well as temperature distribution in the bio-media, and description of various types of applicators and temperature sensors used in microwave hyperthermia/ablation therapy are given. Furthermore, clinical applications of hyperthermia/ablation therapy are also discussed. At last, Oncothermia is introduced followed by references, which provide the detailed information on the subject.

2. Mechanisms of Hyperthermia Therapy

The rotation of dipole molecules of water and proteins due to the applied microwave field generates friction between the molecules giving rise to heating of the bio-molecules. The heat is generated due to the significant dielectric losses occurring in the bio-media at microwave frequencies. Due to the generation of heat in the tissues, metabolic rate increases which results in increase of reactive oxygen species. The cumulative effect of heat and the presence of enhanced reactive oxygen species in the tissue causes accumulation of misfolded proteins, alters the structure of plasma membrane and inhibits glycolysis and respiration within the cells. This results in hyperthermia-induced tumor cell death.

3. Microwave Hyperthermia Parameters

Specific absorption rate (SAR), penetration depth (PD), effective field size (EFS) and temperature distribution in the tissue are important hyperthermia parameters. SAR is defined as the power absorbed per unit mass of the tissue. PD is the depth in the tissue where the SAR value is down to 13.5% of the maximum in the tissue while EFS is the area covered by 50 % (-3 dB) SAR contour in the transverse plane.

4. Estimation of SAR and Temperature Distribution within the Tissue

The following techniques are used for theoretical estimation of SAR in the bio-tissues:

a) Plane Wave Spectral Technique [15, 16]
b) Vector Potential Method [17]
c) Green's Theorem Approach [18]
d) Fresnel-Kirchhoff Scalar Diffraction Theory [18]

Among these techniques, plane wave spectral technique is most appropriate for tissue/tumors lying close to the applicator.

Numerical techniques are also available for quantification of fields and hence SAR in the bio-media [19-22]. Some important numerical techniques used for quantification of fields in bio-media are the Method of Moments (MoM), Finite Difference Time Domain (FDTD) method, Finite Element Method (FEM) and Finite Integration Technique (FIT). MoM uses an integral equation for the electric field induced in the bio-media. Important software based on MoM is IE3D from Mentor Graphics (Formerly Zeland Software Inc.). FDTD method solves the time domain Maxwell's equation (Wave equation) for all components of electric and magnetic fields in the entire domain of interest. Important software based on FDTD method are XFDTD software by Remcon Inc. and EMPIRE from IMST. FEM technique solves the Maxwell's partial differential equations in frequency domain. Though it requires large amount of computer memory, it provides very accurate results for any arbitrary 3-D structures with any combination of material properties. Ansys High Frequency Structure Simulator (HFSS) is a very powerful software available using FEM numerical technique. The Finite Integration Technique (FIT) is a consistent discretization scheme to solve Maxwell's equations in their integral form. The resulting matrix equations of the discretized fields can be used for efficient numerical simulations. Transient solver of CST Microwave studio software uses FIT. These techniques have their relative advantages and disadvantages.

The temperature distribution in the tissue/tumor region is estimated using bio-heat equation devised by Pennes [23]. The bio-heat equation represents the relationship between the rate of microwave energy absorbed into the tissue and the increase in tissue temperature.

5. Microwave Hyperthermia Applicators

Important design considerations for design of hyperthermia/ablation applicators are given in the following:

i) Impedance matching aspect between the applicator and the tissue should be considered during its design.
ii) Near fields are more important than far field for coupling microwave energy into the biological systems.
iii) There should be minimum external leakage radiation.
iv) Proper temperature distribution in superficial or deep seated tumors should be produced.
v) The field should be localized (focused) within whole tumor volume without heating surrounding normal tissues.

The heat can be applied in different ways:

- Non-invasive or External
- Invasive or Internal or Embedded

Many types of non-invasive and invasive applicators have been investigated till date including those reported in the reference [9].

Non-invasive applicators are better from the point of view of the patient since they don't cause any injury or pain to the subject. But temperature distributions and changes in temperature at or near the tumor site can be controlled in a better way using invasive applicators.

Non-invasive Applicators

These are used as individual antenna elements (applicable for superficial tumors) or in array configuration (applicable for deep-seated tumors) positioned in direct contact or in close proximity with the body.

Many types of waveguides/horns carrying single mode/multiple modes suitably loaded with dielectric/ water for impedance matching purpose have been designed for producing superficial hyperthermia in ISM microwave frequency bands. Since waveguide/horns are bulky and cumbersome, planar conformal applicators have also been investigated for superficial hyperthermia.

Different kinds of phased array configurations using both waveguide/horn as well as planar elements have been studied for treating deep-seated tumors at microwave frequencies (using ISM frequency bands). Global optimization method (Particle Swarm Optimization) [24] has also been used to optimize both amplitudes and phases of the antenna elements of the array to raise the temperature of tumor while keeping the temperature of healthy tissue at normal body temperature.

Invasive Applicators

Very effective interstitial applicators have been designed and clinically tested for treating accessible tumors of large volume, such as those in esophagus, cervix and prostate or removing a heart lesion through hyperthermia/ablation. The details of different types of applicators including those reported in the literature in recent times will be discussed during presentation of the paper.

6. Temperature Sensors

The objective of hyperthermia/ablation therapies is to selectively heat/destroy the cancerous tumor while keeping the surrounding healthy tissues at normal body temperature. To achieve this objective, monitoring of tissue temperature is done since the killing of tumor cells/irreversible damage of tissue depends on temperature and time of application of the hyperthermic treatment. Various thermometric techniques used for monitoring of temperature of the treated region are divided into invasive (contact) and non-invasive (non-contact) ones [25, 26]. The invasive sensors include thermocouples, thermistors and fiber-optic based sensors. The non-invasive temperature sensors are based on magnetic resonance (MR), Computed Tomography, Ultrasound Imaging and shear wave elastography.

7. Clinical Applications

Numerous clinical trials are being done worldwide to improve the hyperthermia techniques and evaluate the effectiveness of hyperthermia and ablation. Trials are also conducted for combination therapies i.e. hyperthermia combined with other therapies. For the review and details of clinical trials, readers can go through the references [1, 5, 8, 12, 14, 27, 28].

8. Oncothermia

Hyperthermia is not generally accepted as conventional cancer therapy due to complications involved in heating the deep-seated tumors and the requirement of confining the heat through microwave beam only to the malignant tissue region. Oncothermia [29] is a method of hyperthermia in oncology. It controls the locally applied heat by selectively targeting the cellular membrane of the malignant cells. The selection of the method is based on various biophysical and biochemical considerations. Further details of hyperthermia will be presented in the the conference.

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