Application of Microwave Hyperthermia in Oncology

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Abstract – **In this article the basic concepts of microwave hyperthermia are given. The general types of hyperthermia are discussed and results of clinical studies on hyperthermia are given. Types of microwave hyperthermia applicators are presented – single and multielement array applicators. Methods for temperature measurement of body tissues are also given. In the final paragraph there is a short overview of the problems that have to be solved in order to improve the efficiency of the method.**

Keywords – **Microwave hyperthermia, Cancer treatment, Applicators, Temperature measurement.**

I. Introduction

The research of the effects of Electromagnetic Field on biological systems is of growing interest. High levels of electromagnetic radiation are considered harmful to human health that's why many countries have introduced Specific Absorption Rate (SAR) limitations. SAR is a measure of the rate at which radio frequency (RF) energy is absorbed by the human body. ANSI standards introduce safe exposure levels of SAR of 4W/kg. A safety factor of ten is incorporated so the final recommended protection guidelines of a SAR level is 0.4W/kg. However there is a disagreement over exactly what levels of absorbed RF energy is harmless. For instance in eastern European countries SAR thresholds are much lower that the thresholds introduced in western European countries.

Apart from the harmful aspects, Electromagnetic Field has some positive effects when used in medicine in the fields of oncology, physiotherapy, urology, cardiology, surgery, ophthalmology.

II. Microwave Hyperthermia to Treat Cancer

Microwave hyperthermia is procedure of increasing the temperature of the human body or some part of it using microwaves for the purpose of treating medical conditions such as cancer. There are three broad categories of hyperthermia- localized hyperthermia, regional hyperthermia and whole body hyperthermia [1][2]. Using microwaves body temperature is increased in the interval 41 and 45℃.

In localized hyperthermia heat is applied to a small area where the tumor is located using different methods of delivering the energy [3]. Depending on the tumor location there are three approaches to introduce microwave heating:

- External method is used to treat tumors that are located on just below the skin. This approach uses external applicators that are positioned around the appropriate region and microwave energy is focused to raise the temperature of the desired part of the body.
- Intraluminal or endocavitary methods may be used to treat tumors within or near body cavities. This approach is based on inserting probe in the cavity in question for directly heating the tumor.
- Interstitial method is used to treat tumors located deep within the body, such as brain tumors. Imaging techniques such as ultrasound are used to determine the exact location of the tumor. After that, under anesthesia, probes or needles are inserted onto the tumor with high precision. Microwave radiation is then applied to the tumor to increase its temperature with the purpose to kill cancer cells.

Regional hyperthermia is used to treat larger areas of the human body such as a limb, body cavity or an organ [3].

- Deep tissue approaches may be used to treat cancers within the body, such as cervical or bladder cancer. External applicators are positioned around the body cavity or organ to be treated, and microwave or radiofrequency energy is focused on the area to raise its temperature.
- Regional perfusion techniques can be used to treat cancers in the arms and legs, such as melanoma, or cancer in some organs, such as the liver or lung. In this procedure, some of the patient's blood is removed, heated, and then pumped (perfused) back into the limb or organ. Anticancer drugs are commonly given during this treatment.

Whole-body hyperthermia is used to treat metastatic cancer that has spread throughout the body. This can be accomplished by several techniques that raise the body temperature, including the use of thermal chambers (similar to large incubators) or hot water blankets [3].

The effects of hyperthermia on the host and cancer tissue are pleiotropic and depend mainly on the temperature and the physical techniques applied. The biological and molecular mechanisms of these effects are changes in the membrane, the cytoskeleton, the ion-gradient and membrane potential, synthesis of macromolecules and DNA-replication, intra- and extracellular pH and decrease in intracellular ATP. Genes can be up-regulated or down-regulated by heat, for example the heat-shock proteins.

Synergistic effects by interactions with antineoplastic agents, radiation and heat can be several powers of ten even at moderate temperatures. In addition, reduced chemotherapy resistancy, possibly due to increased tissue penetration,

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increased membrane permeability, and activated metabolism, has been observed.

Immunological effects of hyperthermia may play an additional role in cancer therapy such as immunological effects on cellular effector cells (emigration, migration and activation), induction of cytokines, chemokines and heat shock proteins (chaperones), and modulation of cell adhesion molecules. The induction of heat-shock proteins might increase specific immune responses to cancer cells.

There are three most common ways to use hyperthermia- heat alone, combination of heat and radiation, combination of heat and drugs [1].

Heat alone

This method is based on directly killing the malignant cells using high temperatures in the interval 41- 42℃. However the thermal response of the cells depends on micro environmental factors such as pH. Main phenomenon justifying this technique is protein denaturation which is happening in the temperature range between 39 and 45℃.

Heat and radiation

Aggregation of nuclear proteins damage is thought to be the central event by which heat makes cells more sensitive to radiation. The synergy between heat and radiation, often expressed as thermal enhancement ratios (TERs), is highest when the two modalities are given simultaneously. When heat precedes radiation, the synergy is lost when the time interval between the two modalities increases; this loss of TERs nicely parallels the decline in protein aggregation.

Heat and drugs

A lot of physiology-related features make a combination of heat and drugs very attractive. Moreover, heat can cause supra-additive killing when combined with alkylating agents, nitrosureas, platinum drugs, and some antibiotics, although for some drugs only additive effects or even less than additive effects on cell death are found. The most impressive results in this regard are for heat and cisplatin treatments. Synergistic killing is already found at rather mild heat treatments.

When cells are exposed at elevated temperatures to drugs, their response is frequently very different from that seen at 37°C. Drugs whose rate-limiting reaction is primarily chemical (i.e., not involving enzymes) would, on thermodynamic grounds, be expected to be more efficient at higher temperatures. The rates of alkylation of DNA, or of conversion of a nonreactive species to a reactive one, can be expected to increase as the temperature increases. Tissue culture studies have shown this to be true for the nitrosoureas and cisplatin. For other drugs, there appears to be a threshold at or near 43°C. Below that temperature, drug activity is only mildly enhanced. At higher temperatures, however, cell killing proceeds at a greatly enhanced rate. The combination of chemotherapy with hyperthermia still deserves attention and has high potential.

III. Clinical results

A study in the Netherlands that used three different systems to deliver hyperthermia found that hyperthermia in addition to radiation may be especially useful in locally advanced cervical tumors [4]. The Dutch study involved 358 patients with bladder, cervical, or rectal cancer, randomly assigned to radiotherapy or radiotherapy plus hyperthermia. For patients with cervical cancer, 3-year overall survival was 27% after radiotherapy alone vs 51% after radiotherapy plus hyperthermia.

A study conducted at nine centers in Europe and North America randomly assigned 341 patients with localized, high-risk soft-tissue sarcoma to neoadjuvant chemotherapy alone or with regional hyperthermia. Patients receiving the combination therapy had significantly better local progression-free and disease-free survival [5].

The results from a study in Czech Republic are also promising. More than 500 patients were treated by combination of hyperthermia and radiotherapy. Complete response of the tumor was observed in 52.4% of the cases, partial response at 31.7% and no response at 15.9%[6].

IV. Microwave applicators used for hyperthermia

Single applicators

Early hyperthermia trials were conducted with single-aperture devices having no ability to steer or focus energy other than shifting patient position relative to the applicator. These trials included 27 MHz ridged waveguide, 82 MHz helix, 70 MHz coaxial TEM applicator, and 27 to 70 MHz evanescent-mode waveguide excited below the cutoff frequency by entering a resonant circuit (lumped capacity and inductance) with a wave impedance build-up band-pass filter for the operating frequency. Most of the microwave equipment includes a water bolus for surface cooling. Low-profile, light-weight microstrip applicators, which are easier to use clinically, are also used. The type of applicator selected depends on the production of sufficient thermal field distributions at different depths of the tumor in a variety of anatomical sites. Single-element applicators can safely deliver optimum thermal doses to relatively small superficial tumors. Over the years, several types of applicators for external local hyperthermia have been investigated by many researchers based on the principle of a dielectric filled waveguide or horn antenna [1].

Multielement Array Applicators

To increase the value of the SAR at depth relative to the surface SAR in hyperthermia therapy, we must geometrically focus energy deposition from multiple E fields generated by an array of applicators [1]. A basic array for external deep heating will likely consist of an annular ring of radiating apertures. The parameters of interest are the external E field within an array at the surface of the patient's body, the SAR pattern within the target volume, and the radiation leakage levels of the scattered fields around the applicator. Several different RF electrode arrays have been investigated. Two arrays of needle electrodes arranged in two planes, with a bipolar RF current between the arrays were examined. In the bipolar system, RF current is passed between two electrodes instead of between a single electrode and a ground path, so two electrodes heat the tissue instead of one, resulting in a larger ablation zone. Other groups investigated different array configurations, and segmented needle electrodes have been suggested to allow for better control of tissue heating. An array of applicators with variations in phase, frequency, amplitude, and orientation of the applied fields can add more dimensions to controlling the heating patterns during hyperthermia cancer therapy. Because of the constructive interference of E fields at the intended focus and destructive interference of E fields away from the focus, multichannel coherent phased-array applicators can theoretically provide deeper tissue penetration and improved localization of the absorbed energy in deep-seated tumor regions without overheating the skin and superficial healthy tissues, compared to single or incoherent array applicators. When comparing array applicators with a single applicator, array applicators provide deeper tissue penetration, reduce undesired heating of normal surrounding tissues between the applicator and tumor, and improve local control of the tumor temperature distribution. Heat generated by RF devices is delivered regionally across a much larger area. However, a microwave array system requires target compression because of the shallow penetration of the higher microwave frequencies. RF array applicators surrounding the body are used in attempting to heat deep tumors. However, studies in external RF array thermotherapy have shown the difficulty of localizing RF energy in malignant tissue deep within the human body without damaging superficial healthy tissue due to hot spots. Improvements in RF energy deposition are achieved when the RF phased array is controlled by an adaptive algorithm to focus the RF energy in the tumor and tumor margins, while the superficial RF fields are nullified. Clinically, the use of phased arrays as heating applicators has several advantages. Phased arrays can easily compensate for the effects of inhomogeneities of the treatment volume (which includes the tumor and the surrounding tissues). The heating pattern can be controlled electronically, thus eliminating the need for mechanical movement of the applicator head. This simplifies the machine-patient interface and allows for better use of the available power. Also, electronic switching can be performed rapidly, thus enabling swift response to changes in the tumor environment. However, clinicians cannot always accurately predetermine or manually adjust the optimum settings for output power and phase of each antenna to focus heat reliably into deep-seated tumors. Two outstanding challenges in EM phased-array hyperthermia are (1) to selectively elevate the temperature in the cancerous tissue without excessively elevating the temperature of the surrounding healthy tissues in the presence of electrical and thermodynamic inhomogeneities, and (2) to react to unexpected changes in the patient positioning and physiology (e.g., sudden change in blood flow in the tumor) that can significantly impact the quality of the delivered treatment. Significant research progress has been obtained recently in heating devices appropriate for deep hyperthermia including ultrasonic arrays, RF arrays, and microwave arrays.

V. Temperature measurement

The choice of a particular thermometry system should be made following careful consideration of its intended application. Any measuring instrument can be considered acceptable for a given purpose if the error contributed by the instrument is small compared to other errors or uncertainties in the measurement. Hence, in local hyperthermia where large temperature fluctuations are encountered, an extremely accurate thermometer may not be required. An overall error not exceeding 0.3°C is probably acceptable, but achieving this accuracy in a clinical environment may require that the thermometer agree with an institution's standard to within 0.1 or 0.2%. In whole body hyperthermia, on the other hand, where temperatures are only a few tenths of one degree below the lethal limit and homogeneity is excellent, instrument errors of more than +/-0.05% may be unacceptable [7].

Temperature control by microwave radiometry

Human tissues spontaneously emit electromagnetic radiations of thermal origin which can be measured by a very sensitive receiver called “a radiometer”. When this measurement is carried out in the microwave frequency range, it is possible to evaluate the tissues temperature. Microwave radiometry is used to detect thermal anomalies inside the human body but also to evaluate, noninvasively the temperature of the body. In the microwave domain, the thermal noise power emitted by the body is directly proportional to the temperature and can be obtained by integrating the spectrum brightness B(f). The temperature of a dissipative body can thus be determined by a measurement of the electromagnetic power radiated in a given frequency bandwidth. This measurement is achieved by systems which use an antenna as an electromagnetic power captor in the microwave region [8].

Temperature measurement using thermocouples

Thermocouples are used as invasive thermometers in clinical hyperthermia. The probe is inserted in the area of interest and the temperature is measured directly [8].

For measuring the surface body temperature an infrared camera may be used.

VI. Future Challenges

Although a lot has been done in the field of microwave hyperthermia, there are still many obstacles to be overcome. Some of the major technological challenges that make hyperthermia therapy complicated are the inability to achieve uniform temperature distribution in a tumor, inability to precisely monitor the temperatures of the tumor and the healthy tissue and wavelength limitations.

To achieve uniform temperature in the tumor and to focus the electromagnetic energy in the tumor alone and not in the surrounding tissues, more sophisticated applicator designs are required. To face this challenge more work has to be conducted by examining how electromagnetic energy propagates through the human body and determining optimal radiation patterns for the applicators.

In order to have more concentrated beam of energy a higher frequency wave must be used. From the other hand it is known that the penetration ability on the waves decreases for shorter wavelengths. This leads to limitations on the frequencies to be used. For superficial tumors higher frequency wave can be used. If we want to achieve deeper penetration however a radio wave with lower frequency must be used.

Very important part of hyperthermia is to monitor the temperature of the tissues during the treatment. There is a limitation to monitor the temperature at the same time the tissue is being subjected to RF radiation because the RF field might interfere with the temperature measurement equipment. This prevents real time temperature measurements and is a drawback for temperature control. Improvements in this area are also necessary to increase the control over the process of heating.

As a conclusion it’s evident that a lot of research must be conducted before a fully functional equipment for microwave hyperthermia is created and released for general usage.

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