



International Journal of PharmTech Research

CODEN (USA): IJPRIF, ISSN: 0974-4304 Vol.8, No.6, pp 292-299, 2015

Hyperthermia Techniques for cancer treatment: A Review

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Abstract: Cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body. It is a major cause of death, and its incidence is increasing every day. Various methods and protocols used which include chemotherapy, radiology, surgical removal of the tumor, etc. But these methods have many side effects that make patients feel unbearable pain and inflict deep anxiety. Over the past decades, there is a struggle to discover new techniques to fight against cancer. Hyperthermia is an old therapy of treatment that gives a new hope and which when combined with engineering techniques proves one of the best cancer treatment options. This paper reviews the relevant information for the combination of various engineering techniques with hyperthermia that are well organized according to the methods used e.g. Ultrasonic Hyperthermia; external Radio-Frequency Devices; Hyperthermic perfusion; Frequency Enhancers; apply heating to the target site using a catheter; Microwave hyperthermia; injection of super paramagnetic and magnetic nanoparticles. **Key words :** Cancer, hyperthermia, ultrasonic, radio frequency devices, hyperthermic perfusion, microwave, magnetic nanoparticles.

Introduction:

Cancer is a class of disease characterized by uncontrolled growth and spreading of abnormal cells. If the abnormal cell growth is not controlled, it can result in death. There are over 100 types of cancer diseases that are classified according to the cell type that is initially affected. According to the GLOBOCAN and World Health Organization statistics, in 2012 there were 14.1 million new cancers cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis)[1]. Worldwide around 57 %(8 million) of new cancer cases, 65 %(5.3 million) of cancer deaths and 48 %(15.6 million) people are living with cancer in the span of 5years [2]. According to the annual report provided by American Cancer Society in 2014, there will be an estimated 1,665,540 new cancer cases diagnosed and 585,720 cancer deaths in the US [3]. Cancer remains the second most common cause of death. Many new strategies have been discovering to fight against cancer. These include hyperthermia also called thermal therapy, biological therapies like immunotherapy, photodynamic therapy, laser treatment, gene and inhibitors of angiogenesis. But most of the techniques still need optimization. Hyperthermia is one of the most popular research technique which when combined with engineering bring new hope to cancer patients and adopted as a promising therapy among the alternative methods. From the last two decades, the complement of chemotherapy and radiation therapy is hyperthermia that offers the advantage of eliminating drug resistance and radio resistance tumor cells as shown in figure1.

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Figure1: Hyperthermia for tumor cell death

Various clinical experiments have investigated hyperthermia in combination with radiation or chemotherapy that focus on the treatment of various types of cancer including sarcoma, melanoma, brain, lung, cervix, esophagus, breast, bladder, rectum, liver etc. Many different methods of hyperthermia treatment including local, regional and whole body temperature as shown in figure 2 are currently under study. This paper review various techniques used in these three different methods of hyperthermia.



Figure 2: Different Methods of Hyperthermia

Literature Review:

Depending upon the combination of engineering techniques with hyperthermia this paper presents a review of various methods used in three different types of local, regional and whole body hyperthermia methods. Various types of external applicators are designed which uses the different frequency range of electromagnetic spectrum. The Frequency enhancers, Ultrasonic techniques, use of Microwaves and Magnetic Nanoparticles inserted in body tissues, are a wide area of research today.

Techniques Used:

1) Ultrasonic Hyperthermia:

Absorption of ultrasound waves which involves the propagation of sound waves at a frequency of 2-20MHZ through soft tissues results in heating of medium. Ultrasound has the best combination of small wavelength and corresponding attenuation coefficient with the ability to focus power into regions of small size. Simulation using interstitial ultrasound transducer gives the adequate penetration that could be achieved by driving small cylindrical transducers of outer diameter of approximately 1mm at 6-10MHZ [5]. The designed

ultrasonic therapy system dedicated to breast cancer treatment is a cylindrical shape having a stack of rings, and each ring has up to 48 transducers mounted inside of rings and directed towards the center. The design operate in one of the frequency band (1.8-2.8 MHZ and 4.3-40.8MHZ) arranged alternatively in each ring. The 3D simulations show the excellent capability to achieve temperature distribution of 41.5-44°C[6]. The feasibility of localized lung hyperthermia at depth via therapeutic ultrasound method is described using breathable perfluorochemical liquids as acoustic coupling media in the lung. The ability to use both convective lung hyperthermia and liquid-filled lung ultrasound hyperthermia provides flexibility in heating patterns for hyperthermia treatment of lung cancer [7]. A methodology for building a realistic brain phantom for interstitial ultrasound low dose thermal therapy of brain is proposed which gives the results that envisage the use of phantom for treatment planning and MRI based temperature distribution [8].

2) Hyperthermia with external radio frequency devices:

To compute the specific absorption rate (SAR) in hyperthermia treatment and planning of tumors the electromagnetic field modeling in three dimensions is presented [9]. Different waveguide structures operating in the frequency range of 100-2000MHZ are used. Experimentally three dimensional (3D) numerical models are established to calculate electric field integral equation (EFIE), magnetic field integral equation (MFIE) to compute the SAR in a tumor. The Gaussian beam model (GBM) is used to present accurate source model that shows how aperture and incident fields may be determined. The result shows that GDM is a very good method for characterizing applicators used in hyperthermia for cancer treatments.

The aim of hyperthermia is to raise the temperature in targeted area by approximately 43°C for up to one hour without heating or damaging the adjacent normal tissue A model predictive controller (MPC) in which thermal dose in hyperthermia cancer treatment is developed and can be elevated using simulations with one dimension and one point model of a tumor is demonstrated [10]. In this technique there is direct control of the thermal dose instead using of elevated temperature for therapeutic application. The direct control of thermal dose is done by using a feedback pulse. The simulations are done with different blood flow rates in the tumor with one point or one dimension. An experimental set up of soft heating in hyperthermia is shown as when we apply heat to the tumor part there is a possibility that part of a tumor remains active as there is difference in temperature between central and marginal region. Therefore for providing exact temperature range at each position a heater with a driving mechanism is developed. In this setup there, sensitive magnetic materials are embedded in the body that is heated by application of an external high-frequency magnetic field. Also, it is drive by the rotational field. Because of its capability to move to the tumor this heater can heat the entire tumor within 40 minute, 18.8mm*10.6mm heating area above 45°C is achieved [11]. A conformal microwave array (CMA) applicator that use a temperature controlled water bolus is used to treat breast carcinoma [12]. A computation is done on simulation tool SEMCAD which is a 3D solver based on finite difference time domain (FDTD) method. Results are compared at 915MHZ and 2450MHZ of frequency. An eight element circular annular phase array(APA) consisting of either 915MHZ and 2450MHZ half wavelength dipole elements is placed at 1mm from a cylindrical phantom that provides the interaction between human body tissues and electromagnetic field. For the treatment of cancer of the cervix, prostate and esophagus single endoscopic probe is used which provides a combined process of 3D visualization of target tissues and hyperthermia treatment. The endoscopic probe is real time 3D probe having 1cm diameter with 504 active channels using the frequency of 5MHZ. A finite element mesh is constructed over 128000 elements to create a temperature rise of 4°C within 5 minutes and to get hyperthermia region of 41°C. For the effective treatment heating must be uniform over the completely targeted region. But by using this probe maximum heating is only within 1mm diameter that is not sufficient for treatment. So some work must be involved in modifying the model to increase the transmitting efficiency and to obtain the stability. An early stage breast cancer is effectively cured by using a method of optimal constrained power focusing (OCPF) to design an array of antenna where focusing is done at microwave frequency [13]. OCPF method is proved to be more capable of achieving maximum power deposition in a target position by keeping power level below predetermined level of healthy tissues. The focusing is done in 1to 3 GHZ frequency [14].

3) Hyperthermic Perfusion:

In regional hyperthermia a part of the body such as a limb or an organ is treated with heat. It is a very common technique that is used with chemotherapy or radiation therapy. In the regional perfusion with the help of surgery, the blood supply from a particular part is isolated. The blood is pumped into a heating device and then pumped back into the art to which heat is applied. A computerized system that automatically monitors and

controls the perfusion hyperthermia process is invented. There is a fluid path between a patient and an external fluid treatment subsystem where the control is through the feedback signal that comes from the sensor that is coupled to the patient [15]. The effects of the combined process of giving a drug with the delivery of heat is proved to be beneficial as it includes increased capturing of the drug by the cell, increased killing of tumor cells at a given level of the intracellular drug and decreased micro vascular density. The experiment also predicts that there is less diffusion of the drug to the surrounding tissues that are very small as of the order of 0.48mm [16]. For the treatment of ovarian cancer, the survival rates of Hyper thermic intraperitoneal chemotherapy (HIPEC) at different time points is presented and the results show a potential survival benefits [17]. The Continuous Hyperthermic Peritoneal Perfusion Chemotherapy (CHPPC) for the treatment of malignant peritoneal mesothelioma is described. The malignant mesothelioma of the peritoneal is a very uncommon tumor and even its diagnosis is quite difficult due to which the treatments are not standardized. The results show that the survival rate and the condition of the patient are good enough after CHPPC [18].

4) Hyperthermia uses frequency enhancer:

Living tissues shows the limitation of less absorption at KHz range of frequency. However Ultrasound with a frequency of 20 kHz when combined with i.v injected polystyrene Nanoparticles will enhance the delivery of chemotherapeutic agent 5- fluorouracil. Ultrasound irradiation when combined with Nanoparticles and drug injections will not only result in decreased tumor volume but also complete tumor regression at optimal irradiation condition. A technique that is used for local hyperthermia for the treatment of both focal and metastatic tumors is proposed [19]. A method for enhancing the absorption of RF energy and microwave radiations in living tissues by adding biocompatible fluids and solutions is invented. Dissolved salts of alkali metals, Fe, Mg and Cr in sufficient concentrations can enhance heating of the solution. Different mechanisms like resistive heating and ion cyclotron resonance when combine will provide significantly RF absorption [20]. A transceiver for coupling the RF energy to the target area is invented. The transceiver consists of transmission head, transmission inductor, RF generator, RF absorption enhancer, receiving head, receiving inductor and two tuned circuits. With this arrangement RF absorption is enhanced by injecting an aqueous solution containing suspended particles of electrically conductive material [21]. An invention of frequency modulated hyperthermia technique in which RF absorbing particles are injected into the patient's body is presented. These antibodies are not only enhancing the RF absorption but also the effect of hyperthermia. The multi-frequency hyperthermia is used to generate RF signal that is frequency modulated. The center frequency of FM hyperthermia is normal sized particles that are used as energy absorption enhancer and modulation of FM hyperthermia generates frequency corresponds to size tolerance of particle [22]. A system of delivering radio frequency electromagnetic field at 13.56MHZ for Heating of Citrate Coated Gold Nanoparticles for Cancer Therapy is developed. The heating is both size and concentration dependent, it has been shown that with 5 nm Particles producing a 50.6±0.2°C temperature rise in 30 s for 25 µg/mL gold (125 W input). The results show significant enhancement of cancer cells death when gold Nanoparticles are added [23].

5) Hyperthermia using a catheter:

An apparatus which includes a catheter with fluid dry passages so that the microwave antenna applicators and temperature sensors are inserted for measuring the temperature of prostate tissue is invented .The electromagnetic generator gives energy to the applicator. To calculate the heating effect a comparator is connected to the temperature sensor to the other terminal of which temperature reference potentiometer is connected for comparing the actual temperature of tissue with the desired temperature [24]. An invention uses microwave energy with an instrument that includes a collinear array of antenna to transmit EM energy in frequency range between 0.3 and 10 GHz and a power level in a range between about 100 mw and 150 W is presented. The instrument also includes directive elements with radiating elements to enhance the energy, temperature sensor to sense the temperature of a location, and a catheter that includes a balloon at distal end which is formed of a material that makes transmission of electromagnetic energy [25]. A catheter based ultrasound applicators which is an optimized thermal treatment platform which provide feedback for applicator selection, positioning which gives proper angle or orientation, an optimal initial power setting that altogether improve the delivery of hyperthermia treatment is presented [26].

6) Microwave hyperthermia:

It is one of the promising techniques that has been used on thousands of patients suffering from prostate or breast cancer. Microwave energy is effective in heating cancerous tumors because tumors have high water content. One or more microwave antenna can be used to treat tumor that depend on tumor size and location in the body. Microwave hyperthermia has utilized single waveguide microwave antenna working at 434,915 and 2450MHZ [27]. A 2D finite element analysis for the treatment of pathological human tissues containing tumors is presented. The analysis compares the model of coaxial antenna with one, two and three air slots. The model is based on TM mode coupled with Penne's equation under a transient state condition. The operating frequency of antenna using is 2.45GHZ [28]. A zero order mode resonator (ZOR) metamaterial (MTM) structure for microwave thermotherapy to generate and radiate a plane EM wave into treated biological tissue that can produce a homogeneous SAR distribution in the plane parallel to applicator aperture is generated .ZOR principle is simulated on COMSOL software that shows a very good SAR homogeneity and achieves a penetration depth close to that of EM plane wave [29]. A method of microwave hyperthermia by utilizing thin microwave antenna located in human tissue is described. For the numerical simulation finite element method (FEM) is used. The results present a simple methodology of finding best model parameters for the optimal interstitial microwave hyperthermia treatment [30].

7) Hyperthermia with the injection of super paramagnetic and magnetic nanoparticles:

A localized heating of tumor cells by injecting super paramagnetic Nanoparticles are not only biologically acceptable by the body but biodegrable also is presented. The temperature increase is induced by high frequency magnetic field and is controlled by close loop temperature control feedback system. The results show that with the temperature increase of 45oC the growth of CT-26 Colon cancer cells starts degrading [31]. A model of realistic breast is demonstrated in which super paramagnetic Ferro fluid is injected into a breast tumor and by applying external electromagnetic field excitation hyperthermia treatment is provided. During the procedure a panes bio heat equation is used to describe the magnetic fluid hyperthermia and the experiment is done on the three layer female breast phantom and numerical modelling of which is done in two successive steps. First magnetic fluid simulation and second heat transfer equation. The simulation result shows that model of mixture containing the magnetic fluid and tumor tissue is most important consideration and this gives better results and provides accurate temperature control for a tumor with minimal side effects [32]. For providing better target potential thermal characteristics of magnetic Nanoparticles Fe2O3 mixed with gelatin under the radiofrequency magnetic field is described. Various factors that effect the thermal properties like frequency of radio wave, the concentration of particles, the magnitude of applied field, the level of temperature etc. are calculated. But with concern of surrounding tissues more work has to be done in this field for improving heating efficiency of target and surrounding tissue and to make this technique more acceptable in hyperthermia treatment planning [33]. Magnetite is the magnetic nanoparticle that is targeted to tumor tissue to which heat is applied using external alternating magnetic field through Neel relaxation loss of magnetic nanoparticles. The results of also suggest a research area in which this technique will be beneficial to tumors at distant sites [34].

Conclusion and Discussions:

The experimental results of studies prove that hyperthermia is both the ideal complementary treatment to and a strong sensitizer of radiotherapy and many cytotoxic drugs. With the Ultrasonic hyperthermia the treatment of superficial and deep region tumors that include surface lesions, head and neck is possible. Using this technique heating is possible up to 5-10cm depth with the single transducer and up to 20cm depth with the multiple transducers. For the treatment of prostate cancer hyperthermia with external radio frequency devices is a good alternative although the methods are non-specific for tumor cells. The methods used are very simple as they are used to transmit electromagnetic energy as close as possible to tumor site. Hyperthermic perfusion is used to treat cancer in arms, legs or in some organs of body. To increase the treatment response and reducing side effects frequency enhancers and catheters are used. Microwave hyperthermia is used for the treatment of superficial tumors in breast, limb, prostate and brain. It is one of advance technology in which heating large volume is possible with specialized antennas. But at high penetration localized heating, temperature measurement is difficult. The advantage of paramagnetic and magnetic Nanoparticles has the potential to reduce or eliminate the possible side effects by achieving accurate target doses. The cancer therapy based on nanotechnology is also called special for of interstitial thermotherapy with the advantage of selective heat deposition to tumor cells. This mediated thermal therapy promises to change very foundation of cancer diagnosis, treatment and prevention. An increasing research relates to targeting techniques, delivery strategies

and radiation dose enhancement are likely to energies this field in the coming years. To get more promising results clinical trials still require refinement of techniques which is needed to increase the efficiency.

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