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Ultrasonic Hyperthermia for Cancer Treatment

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ABSTRACT

In this paper, design of transducers, ultrasonic focusing techniques and temperature monitoring for hyperthermia are described. Efforts being made at National Physical Laboratory, New Delhi, on the development of an indigeneous ultrasonic hyperthermia and non-invasive temperature monitoring systems are disscussed.

1. INTRODUCTION

Hyperthermia, a therapeutic technique which uses heat–more precisely elevated body temperatures ($\geq$ 42.5 °C) – has received increasing attention in recent years. From the clincian's point of view, hyperthermia appears to be synergistic with radiation therapy and chemotherapy, and hence enhances the effects of these modalities in the treatment of cancer. Therefore the major role of hyperthermia in cancer therapy is as an adjurant to these major forms of therapy[1-4].

The use of heat for cancer therapy is as early as 3000 BC when cautery was used as means of rapid destruction of the cancerous tumours cells and when temperatures of 5-20°C above normal body temperatures were used. In recent times, it was suggested (usually credited to Busch[5]) that relatively low temperatures might have a therapeutic effert on cancer. Busch's paper was important because it was the first to indicate that temperature, which the normal tissues tolerated, might selectively destroy tumour tissues. Fortunately, there were several other reports of similar regressions of tumours due to high fevers, which generated a lot of interest to find artificial means of inducing elevated temperatures in cancer patients. In the United States, Dr William Coley began to synthesise bacterial toxins which induced high fever in the cancer patients[2-5].

The discovery of ionising radiation in 1895 led to use of radiation therapy as a cancer treatment modality. This resulted in a decreased interest in the fever therapy. Clearly, fever therapy had a major drawback; each patient responded quite differently to a toxin, while radiation therapy tended to give more reproducible results.

1.1. Hyperthermia Techniques

Use of hyperthermia techniques either alone or in combination with other techniques in the treatment of cancerous cells has received attention among the biophysicists and medical practitioners in the recent years[7-13]. Since diseased tissues are sensitive to heat, a number of techniques have been used for clinical hyperthermia. These include water and wax bath immersion[8], perfusion with extracorporeally heated blood[9], and the use of microwave, electromagnetic radiofrequency currents and ultrasound[10-11]. It has, however, been found that ultrasound is more useful for clinical hyperthermia due to its short wavelength (1 mm) and deep penetration depth ($\approx$cm). Due to the short wavelength and deep penetration nature, several methods have been employed for clinical hyperthermia using ultrasound which include plane transducers with skin cooling capable of heating the selective tissue depths, and an array of unfocused transducer[14] for heating deeper tissue depths. Ultrasound system with focused transducer[12] is used for heating of desired volume of tissue at depth. The focused ultrasound does not damage the surrounding normal tissue. A block diagram for a particular ultrasonic tumour therapy system is shown[13] (Fig. 1).

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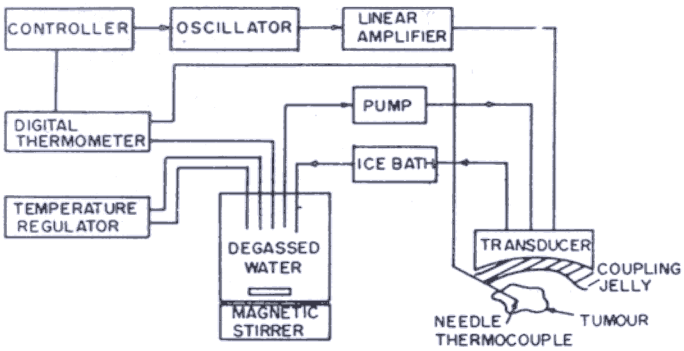

Figure 1. Block diagram of ultrasonic tumour system.

2. COMPARISON OF VARIOUS MODALITIES FOR CANCER THERAPY

Radiofrequency, in the ranges of 0.5 to 30 MHz is good for the local treatment but thermometrically is poor and heating pattern is not uniform. By this simple technique superficial tissues are treated better. The technique is expensive and high power is required.

Microwaves have the frequency range 1-100 GHz, good penetration and a good focusing ability. The local treatment is very good when the microwave co-axial applicators are used. One drawback here is that the heating pattern due to radiation sources is difficult to be analysed.

Ultrasound in the frequency range from 0.5 to 3.0 MHz has an excellent focusing ability and is very good for the local treatment. In this low cost modality, enhancement of biological effect of temperature by a non-thermal mechanism is possible. It has good penetration in soft tissues but large reflection is seen at the soft tissue interfaces.

It is well accepted that temperature in the appropriate range destroys tumour cells and is beneficial to the patient. Measurement of the resulting temperature also becomes easy. Most of the methods employed for producing hyperthermia are based on ultrasound modalities[2].

In ultrasound technique, ultrasonic probes are directly coupled on to the body tissue, where heat is produced by increasing kinetic energy of the molecules. The absorption of ultrasound is inversely proportional to its frequency; the superficial lesions are heated with high frequency waves while for deep seated lesions, low frequency (long wavelength) ultrasound waves are used. The heat absorption at any point in the tissues depends on ultrasonic intensity[6].

Some of the merits[6] of ultrasonic hyperthermia, the most suitable modality for cancer therapy, are (a) deep seated tumours can be treated, (b) tumours absorb ultrasound energy better than normal tissue, (c) beam focusing devices are available, thereby, multiple beam can be directed at deep seated targets without much overheating of nornal tissues, (d) thermometry is easier, and (e) handling the equipment is easy and no special protective measures are required.

3. PHYSICAL ASPECTS OF HYPERTHERMIA

Ultrasound is a form of mechnical energy that propagates through the tissues as a pressure wave. It is generated by the application of a high frequency voltage across a piezo-electric transducer. Frequencies in the range of 0.5-10 MHz are most commonly used for medical purposes. The velocity at which an ultrasonic wave propagates through soft tissues is about 1500 m/s (the mean value at 37 °C is 1570 m/s in nonfatty, soft tissues and 1430 m/s in fat). This leads to wavelengths of 3 and 0.15 mm and 10 MHz respectively.

As an ultrasonic beam travels through tissue, the total energy in the beam is attenuated. In a homogeneous medium, the energy is perfectly collimated beam would decrease exponentially with the distance travelled in the tissue. The intensity at a position r in the tissue is given by

$$I = I_0 e^{-ur} \qquad (1)$$

where I_0 is the intensity at point $r = 0$, and u is the intensity attenuation coefficient. The two main sources of energy loss are absorption and scattering. It is the absorption that leads to the direct generation of heat. Some of the energy scattered out of the primary beam will be absorbed else where in the tissue (for detailed discussions see Coakley and Nyborg[18], and Dunn and Pond[19]). The interaction of ultrasound with tissues can broadly be divided into two classes of mechanism; those due to heating and those due to non-thermal effect[14].

The main non-thermal mechanisms thought to occur in tissues are due to cavitation[16-18], acoustic streaming and radiation force[19]. There is evidence that these effects may be additional benefits in cancer therapy[20].

The intensity of an ultrasonic beam is defined as the energy fluence and is usually specified in W/cm^2. In conventional ultrasonic physiotherapy, spatial intensities average upto 3 W/cm^2. For pulse echo

diagnostic ultrasound, intensities averaged[14] over space and time are typically about 20 MW/cm^2.

The space-averaged intensity in an ultrasonic therapy beam may be measured using a radiation balance[21,22]. Beam profiles are measured using small pressure sensitive hydrophones, or small heat sensitive devices.

Since ultrasound is rapidly attenuated in air at the clinical frequencies, a coupling medium is required between the ultrasonic transducer and the tissue to be treated. It is essential that no air pockets exists between the irradiating head and tissue.

4. BIOLOGICAL ASPECTS OF HYPERTHERMIA

Biology made hyperthermia look promising as an anti-cancer modality, and it seems as good today as ever it did[23]. Some biological aspects of hyperthermia are discussed in the following sections.

(a) Thermal Dose

The concept of thermal dose expresses all heat treatments in terms of equivalent minutes at 43 °C; based on data from cells in culture and normal tissues in mice.

(b) Hyperthermia and Radiation

Researchers have shown that heat inhibits the repair of radiation damage not by inactivating repair enzymes, but by modifying the structure of DNA so that radiation damage is masked.

(c) Hyperthermia and Drugs

There is a wealth of experimental evidence to show that heat enhances the cytotoxicity of some chemotherapy agents, including the alkylating agents, the nitrosoureas, as well as blecomycin and DDP.

In general, there is no cross resistance between heat and drugs, i.e., mutant cells resistant to heat are not necessarily resistant to drugs and vice-versa. An exception is amphoterein-B, for which there is complete cross resistance. The action of this drug involves a membrane effect, and the fact that there is cross resistance between heat and drug in this case is a good evidence that the membrane is involved as an initial target in heat damage.

(d) Thermotolerance

At the basic research level, experiments indicated that thermotolerance is not a consequence of a more efficient repair. At the pragmatic level, it was suggested that vascular thermotolerance may account for the lack of vascular damage seen in human tumours. Also, it was observed that multiple exposures to heat in the human beings are not necessarily advantageous over a small number of exposures. Themortolerance is modified by environmental factors such as p^H, by a host of different membrane-active chemicals, by protein-synthesis inhibitors such as cycloheximide, and by polyamine depletion.

(e) Heat Shock Proteins

A compelling case was made for a close association between heatshock proteins and thermotolerance, based on experiments where there is a correlation between the demonstration of heat-shock proteins by electrophoresis and resistance to heat by clonogenic assays.

(f) Manipulation to Enhance Heat Damage

A number of strategies were suggested that might lead to an enhancement of the biological damage produced by a given exposure to heat. Three particular strategies deserve mentioning.

(i) *Hydralazine*: This drug is a vasodilator and causes blood flow to increase in the normal tissues. As a consequence, blood is diverted from the tumour, leading to an increase in heating and a concomitant increase in heat damage.

(ii) The use of glucose reduces p^H in tumour cell and consequently increases heat demage.

(iii) Step down heating leads to a greater enhancement of the TER in the tumours than in normal tissues.

5. TRANSDUCERS AND FOCUSING IN HYPERTHERMIA

5.1 Transducers

The transducer is a vital component of an ultrasonic probe. It is a device for converting energy from one form into another. In ultrasonic applications, the conversion is usually between the electrical and mechanical forms. A transducer consists of a suitably mounted quartz plate with a frequency (equal to the electronic oscillator), of 1 MHz or above.

5.1.1 Ultrasonic Transducers

Ultrasonic transducers for medical therapy are usually made from a piezoelectric material such as lead

zircoate titanate 4 (PZT 4). The device is driven to vibrate in its thickness mode. (Radial mode of vibrations are also possible, but these generally occur at low freqencies). For maximum energy output, the transducer element is half a wavelength thick and is backed by air. The efficiency of tranduction (the ratio of acoustical power obtained from the crystal to the electrical power applied) of PZT 4 is typically[14] greater than 50 per cent.

5.1.2 Single Planar Transducer

Single planar disc-shaped piezoelectric transducers of 0.3 to 6.0 MHz frequency, and upto 12 cm in diameter are coupled to the body through an integral water column of 10 to 25 cm long[24] (Fig. 2). The fields from such transducers can be calculated by assuming that the plane faces respond linearly to an applied sinusoidal voltage and vibrate as a whole with uniform amplitude and phase. The resultant field is commonly described in terms of two regions, the near field (Fresnel zone) and the far field (Fraunhofer zone).

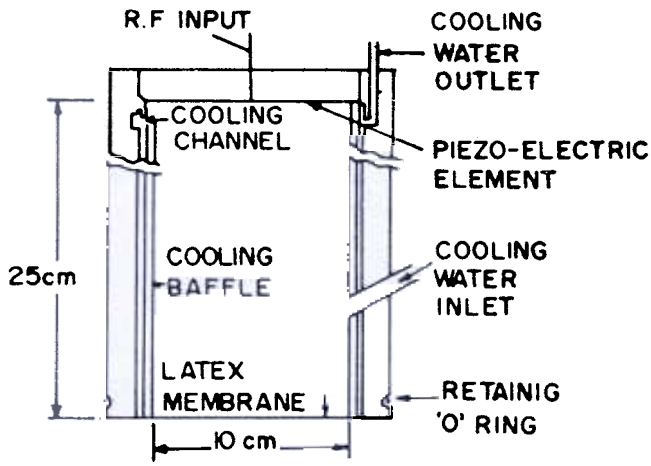

Figure 2. Cross-sectional diagram of a typical single element hyperthermia applicator.

In the near field, interference effects close to the transducer face result in very complex axial and transverse profiles. In the field, the intensity varies smoothly, with the intensity on axis dropping off as the inverse square of distance in a non-attenuating medium. The directivity function D in the far field is given by

$$D = \frac{2J_1 (2a \sin Q/x)}{2a \sin Q/x} \qquad (2)$$

where J_1 is the first order Bessel function, a is the radius of the transducer, Q is the angle that the line joining the measuring point with the centre of the transducer face makes with the axis, and x is the wavelength of sound in the medium concerned.

5.1.3 Multiple Planar Transducer

A multiple transducer adjustable beam system using 6 therapeutic transducers and one diagnostic transducer (Fig. 3) has been evaluated[24] Each therapeutic transducer can be tilted at any angle. It can be planar or focused and can be operated at any of the 9 frequencies between 600 kHz and 6 MHz to obtain maximum absorption within the particular tumour. The frequency of the diagnostic transducer is chosen to minimise any coupling between it and the therapeutic transducer.

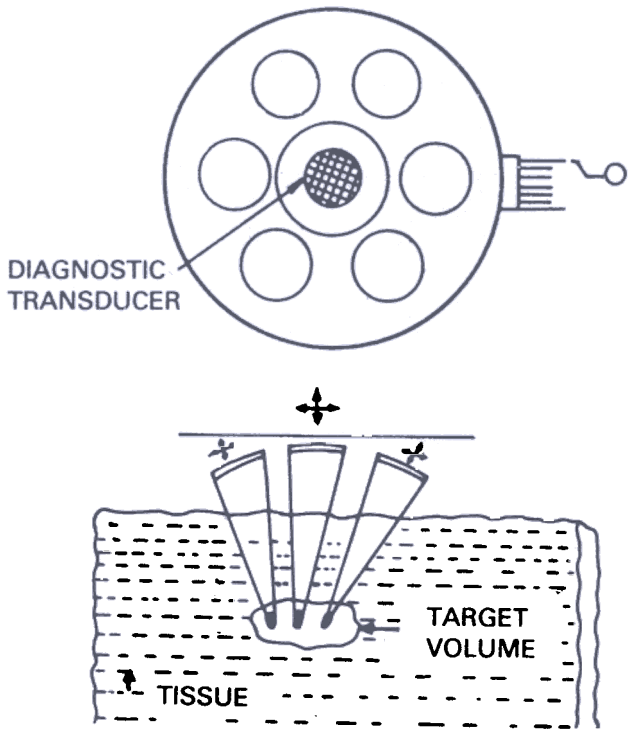

Figure 3. Multiple transducer system for hyperthermia.

5.1.4 Focused Transducer

These generate focused ultrasound waves within a small tumour volume and result into higher intensities at the desired targets with resultant higher temperature. The underlying tissues and bones are unaffected with focused transducer. The maximum depth to which the selective heating obtained is a function of both aperture and frequency.

5.1.5 Scanned Focused Transducer

Focusing concentrates the energy emanating from the tranducer into a small portion which acts as a heat

source. The intensity is controlled externally so as to generate the restricted amount of heat. These multiple focused beams produce multiple hot spots with low temperature in the intervening tissues which are unavoidable with any invasive or non-invasive technique. These hot spots can be moved non-invasively wherever needed without repeated insertions.

5.2. Focusing Techniques for Hyperthermia

Ultrasound has the ability to heat with defined volumes of the tissue using focusing techniques[15]. Focusing of ultrasound beam is obtained mainly with the help of an acoustic lens, a mirror, a shaped crystal or with electronic means[25-26].

Ultrasonic lenses are usually made from solids in which the velocity of sound is greater than in water. Concave lenses are therefore used in order to obtain a converging beam. The easiest lenses to construct are plano-concave[14]. Acoustic mirrors are used in immersion tanks to focus the ultrasound beam and to achieve large aperture and short focal length[25]. Mirror systems are not suitable in general for hyperthermia[14]. Bowl type transducers[27] are used in achieving high acoustic power at the focal point while the ultrasonic axicon[28] which is a combination of a plastic lens and a small conical mirror, is used to get further strongly focused beam[29]. The focus of these transducers lies on the central axis, near the center of curvature of the bowl (Fig. 4). In array type transducers, the mechanical focusing techniques fail and electronic focusing is used, where the transducer array allows the ultrasonic beam to be steered and focused by appropriate combinations of signals associated with each element[30].

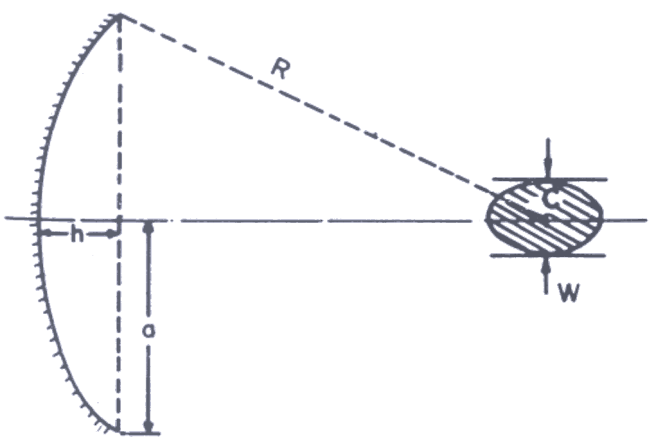

Figure 4. Geometry of a focused bowl transducer c - centre of curvature, h - depth of shell, α - radius of transducer, r - radius of curvature of bowl, w - width of focus region.

6. TEMPERATURE MONITORING IN HYPERTHERMIA

A major - problem in the use of localised hyperthermia for treatment of malignant tumours is to obtain an accurate measurement of the temperature of the tissue being treated. For measurement of tissue temperature distribution in the human body, techniques based on the thermistor, thermocouple and fibre optics probes[33] are used at present. These techniques are invesive.

Thermocouples have generally been employed for measuring temperature elevation during ultrasound irradiations. However, when small objects such as thermocouples are in an ultrasound field in a medium such as tissue, viscous forces acting between the object and tissue will casue an additional local rise in temperature[3]. This will produce an error in any measurement of tissue temperature with invasive probes. To overcome the problem of invasiveness character of these devices, microwave modality was developed but this has limitation[35,36] of penetration depth up to 5 cm. Another non-linear acoustic technique has also been developed for non-invasive measurement of temperature, based on the use of temperature dependancy of non-linear interaction between the ultrasonic wave and the medium. Ultrasonic velocity measured with through transmission technique under different power/intensity ratings of focused ultrasonic hyperthermia system is used as a measure of temperature non-invasively[35] (Fig. 5).

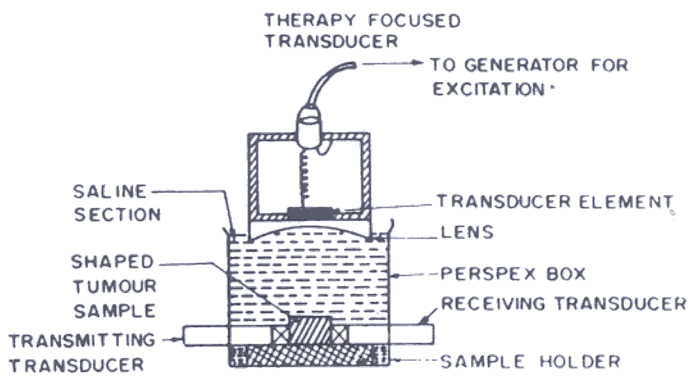

Figure 5. Experimental set-up for non-invasive measurement of temperature in ultrasonic hyperthermia.

7. EFFORTS AT NPL

So far ultrasonic hyperthermia is not made locally in India. Efforts are being made at the National Physical

Laboratory (NPL) to develop an indigeneous ultrasonic hyperthermia. A focusing system has been developed at NPL to be used for ultrasonic regional hyperthermia[6]. This utilises an ultrasonic transducer having a frequency of 1 MHz, but to make the measurements possible in the clinic, more research is required.

8. CONCLUSION

Ultrasonic hyperthermia is the most suitable modality for cancer therapy. So far, work has been done on ultrasonic hyperthermia but a sincere effort is still required for non- invasive temperature monitoring and focused ultrasonic hyperthermia system to make the technique more effective and successful.

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