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Physical and Clinical Aspects of Hyperthermia at Lund University 1989

Bertil Persson, Claes-Ebbe Lindholm, and Torsten Landberg

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Summary

For the induction of hyperthermia in clinical practice in LUND, we developed a 2450 MHz microwave system, which has been used since August 1980. In 1982, we added the frequency 915 MHz, and since 1986, we have also 434 MHz available. A control system based on a computer adjusts the temperature in the tissue by alternating temperature registration and microwave irradiation. Conventional thermistor probes (diameter 0.6 mm), which are placed in the tissue by intravenous cannulas, are used for the temperature reading.

From August 1980 to November 1984 a total of 85 superficial recurrent malignant tumours, mainly adenocarcinomas (78 %), in 38 patients were treated with either combined local hyperthermia, 41-45°C for 4 sessions and low dose radiotherapy, 30 Gy (in 3 Gy fractions) , or the same low dose radiotherapy alone. The treatment was given for two weeks. Hyperthermia was induced externally with 2450 MHz or 915 MHz microwaves. Totally 57 tumours were given combined treatment with a complete and partial response rate of 46 and 30 %, respectively (duration 1 - 38 months). In 18 patients with 2 - 10 superficial tumours each, 56 tumours were used in a comparative study, comparing the effect of combined hyperthermia and low-dose radiotherapy versus the same low-dose radiotherapy alone, the patients being their own controls. The total response rates were 89 and 50 % respectively, in the two treatment groups. The difference in response rates is significant ($p = 0.004$) in favour of the combined treatment, and this is also found when comparing complete remissions only ($p = 0.0027$).

These results encourage us to develop hyperthermia treatment further by using phased applicators and 100 MHz for reaching deep-seated tumours. We also develop methods for non-invasive temperature monitoring.

Introduction

The physical methods for power deposition in local and regional clinical hyperthermia are:

- Thermal convection with a hot water bath, hot air or hot metal
- Ultrasound at frequencies of about 0.3 - 3 MHz
- Electromagnetic fields at radio frequencies RF< 300 MHz
- Electromagnetic radiation at microwave frequencies 300 – 2450 MHz

Several reviews and books on the physics of electromagnetic and ultrasonic hyperthermia treatment have previously been published. In the *AAPM Medical Physics Monograph No. 15 on Radiation Oncology Physics*-1986, Paliwal and Persson (1987) reviewed the physical principles of hyperthermia (Palival and Persson, 1987). That book also describes how to implement a hyperthermia physics program (Palival et al., 1987). Therefore, this presentation will only briefly discuss the different heat-induction methods.

Mechanical heating with ultrasound

Tissue heating with ultrasound is carried out with external transducers, appropriately coupled to the surface of the body. Ultrasound is significantly more penetrating in fat than in muscle tissue. For example, at 1 MHz the penetration depths are 4.4 cm in muscle and 31.3 cm in fat. The short wavelength in tissue, less than a few mm, makes it possible to focus ultrasonic energy in small volumes at large depths. Due to the large impedance mismatch between soft tissue and air, and between soft tissue and bone, these interfaces cause almost complete reflection of the ultrasonic energy. The anatomical locations where ultrasound can be applied are thus limited.

Electrical heating with capacitive radiofrequency RF techniques

The radiofrequency technique, often used in diathermy at the ISM-frequencies (Industrial, Scientific and Medical frequencies) 13.56 MHz and 27.12 MHz, is the application of a pair of capacitor plates excited by the radiofrequency generator.

The tissue is heated due to displacement currents produced by the electric field in the tissue between the plates.

Theoretically, the RF technique has the potential for deep heating in a homogeneous medium. The boundary conditions at a fat-to-muscle layer approximately parallel to the plates will, however, result in preferential heating of the fatty tissue. To obtain a uniform field distribution the plates should be large compared to the distance between them. To overcome the problems with excessive heating of subcutaneous fat layers, multiple pairs of plates are arranged in a "crossfire" configuration (Sugaar and Leveen, 1979).

Inductive radiofrequency techniques

When an oscillating magnetic field is applied to a biological medium, eddy currents are generated that produce heating in the tissue. The most conventional type of applicator is the so-called "pancake" coil often used in diathermy at 13.56 MHz or 27.12 MHz. This type of applicator is suitable for heating rather superficial tissue volumes. Storm and collaborators described a hyperthermia system, (commercially available under the trade name "*Magnetrode*"), consisting of an annular one-turn coil excited at 13.56 MHz for regional deep-heating (Storm et al., 1982).

Radiative electromagnetic techniques

Techniques based on radiative electromagnetic apertures have mostly been used at the microwave ISM-frequencies of 2450 MHz, 915 MHz and 434 MHz. Radiative apertures working at lower frequencies have, however, also been used for regional deep heating. Turner described a technique with multiple phased applicators in a circular configuration (the Annular Phased Array, BSD Medical Corporation) (Turner, 1982).

Hyperthermia system used in clinical practice in LUND

For the induction of hyperthermia in clinical practice in Lund, we first developed a 2450 MHz microwave system, which has been in use since August 1980. In 1982, we added the frequency 915 MHz, and since 1986, we also use 434 MHz applicators (Nilsson et al., 1982, Nilsson, 1984).

A control system based on a computer that adjusts the temperature in the tissue by alternately temperature registration and microwave irradiation. Conventional thermistor probes (diameter 0.6 mm), which are placed in the tissue by applying intravenous cannulas are used for the temperature reading (Nilsson et al., 1982).

For the treatment of superficial tumours, different waveguide applicators have been designed. A temperature increase with acceptable homogeneity can be reached in tumours with a 4 - 6 cm diameter and a depth of 2 - 3 cm below the skin surface (Nilsson et al., 1985).

Clinical Experience of Hyperthermia in Lund

So far the combined treatment of low-dose conventional radiation therapy and hyperthermia has been applied to about 100 patients in Malmö and Lund. At the time of treatment, these patients had superficial, local recurrences of tumours or metastases, in spite of earlier used established treatment of recurrences. The full radiation absorbed dose of 30 Gy (10 fractions á 3Gy) and the hyperthermia treatment (41 - 44 °C during 45 minutes) have been the same for each treatment.

In those cases, where the patients have had more than one superficial tumour, usually the smallest tumour was treated with radiation therapy only, to the same fractionation schedules as in the combined treatment (Lindholm et al., 1982a).

From August 1980 to November 1984, 85 evaluable superficial recurrent malignant tumours, mainly adenocarcinomas (78 %), in 38 patients were treated. The treatment was given for two weeks, with either combined local hyperthermia, 41-45C for 4 sessions, and low-dose radiotherapy, 30.0 Gy (CRE = 13.1), or the same low-dose radiotherapy alone. Hyperthermia was induced externally with 2450 MHz or 915 MHz microwaves.

A total of 57 tumours were given combined treatment with a complete response of 46% and a partial response of 30 %, respectively (duration 1 - 38 months).

In 18 patients with 2 - 10 superficial tumours each, 56 tumours were used in a comparative study comparing the effect of combined hyperthermia and low-dose radiotherapy versus the same low-dose radiotherapy alone. The patients were their own controls. The total response rates were 89 and 50 %, respectively, in the two treatment groups. The difference in response rates is significant ($p = 0.0039$) in favour of the combined treatment, and this is also found when comparing complete remissions only ($p = 0.0027$).

Multiple logistic regression showed that the following factors had prognostic significance

- the time interval between the earlier given radiotherapy and the present RT+HT treatment ($p=0.0002$)

- the average of minimum temperature of the "best" hyperthermia treatment session (p=0.0078)
- the CRE value for the present RT treatment (p=0.0090)5

Thus our data indicate that the average minimum temperature of the best" hyperthermia session is the most important thermal factor for complete tumour response when treated with our combined modality (Lindholm et al., 1985, Lindholm et al., 1982b, Lindholm et al., 1987, Persson et al., 1987).

This thermal factor seems to be superior compared to the concept of thermal iso-effect dose for predicting complete response in our material (Lindholm et al., 1988)

Developments of Phase-Controlled Applicators

In microwave or RF hyperthermia, phase control, in addition to power control, is valuable in improving penetration and spatial homogeneity of the heat deposition (Nilsson and Persson, 1985).

A phantom study has been performed with four independent power amplifiers at 434 MHz, each with 400W power output and phase control well over 360 degrees for each channel. This study verified that the system could focus heat at different locations by changing the relative phases of the four channels (Bolmsjö et al., 1988).

Experimental data were also compared with theoretical calculations using the equivalent current approach (Nilsson, 1984). The results from the phantom measurements showed that the system was capable of focusing heat on preselected regions.

A comparison between experiments and theoretical calculations showed a good correlation except close to the applicator edges, where local hot spots occurred due to near-field interactions.

The phase control method has also been used to treat a large head and neck nodule, approximately 20×10×6 cm (W×H×D). Three waveguide applicators, including water boluses, were positioned around the nodule to cover it completely.

The results of this clinical case study confirmed the potential of using phase control to improve heat penetration. The short wavelength of 434 MHz makes this frequency well suited for hyperthermia treatments where localised heating is preferred rather than regional warming (Bolmsjö et al., 1988).

The study demonstrates that phase control is useful to increase the physical quality of hyperthermia treatments. The next technological step for hyperthermia systems should be to include automatic and continuous phase control so that all parts of the target volume are well heated.

Interstitial and Intra-cavitary Hyperthermia Treatments

Microwave antennas

Placing the heating element directly into the tumour can achieve a therapeutic temperature without appreciable heating of normal tissues, regardless of the treatment geometry. The heating elements we use are radiative coaxial microwave antennas (434 or 915 MHz) placed in catheters.

Temperature fluctuations caused by non-uniform blood perfusion or other in-homogeneities can be reduced by placing a multiplicity of heating devices into the tumour and adjusting the power of each one to the appropriate level. With this technique, one can also generate complex temperature distributions with maximums either in the centre or in the periphery of the target volume.

In intra-cavity hyperthermia, the heating elements are similar to interstitial ones, but the thickness is slightly larger to fit the body cavities in question. Intra-cavity hyperthermia is used for the treatment of gynaecological cancer, rectal cancer and the prostate.

Thermal Self-Regulating Ferromagnetic Seeds

In the treatment of extensive or deep-seated tumours, it might be considered practical to use thermos-seeds which can be placed intra-operatively and need no wires or coaxial feedlines. They absorb energy from an externally applied magnetic induction field in a contactless manner, with each seed acting as an independent and self-contained heating element. Thermal conduction transfers the heat generated within the thermo-seeds to the tumour. For clinical hyperthermia, an array of thermo-seeds is implanted into the target volume, remaining in place for the duration of the entire treatment course. Individual treatments are carried out by placing the patient into a large induction coil operating at the appropriate frequency and intensity.

Thermo-seeds that would reach a predetermined temperature in any tissue environment constant temperature seeds) should produce high- temperature homogeneity, and may eliminate the need for temperature monitoring. This technique can be combined with both external, and interstitial radiotherapy. It is also possible to implant thermo-seeds together with radioactive seeds or to make the thermos-seeds radioactive themselves.

Constant temperature thermos-seeds operate on the principle that a Ferro-magnetic seed produces substantially more heating power in a given induction field than a similar nonmagnetic seed. Hence, if one made the thermos-seeds from a Ferro-magnetic material that would have its Curie-point (the transition from the ferromagnetic to a non-ferromagnetic state) at the desired implant temperature, each seed would act as if it had its own built-in thermostat, generating heat at a decreasing rate as the target temperature is approached. In the design of a hyperthermia system based on the Curie point principle, several factors have to be taken into account. First, the thermo-seeds must be capable of producing enough heating power to assure that therapeutic temperatures can be reached. Furthermore, in order for thermal regulation to be effective, the transition between the magnetic and the nonmagnetic state should occur within a rather narrow temperature range. To keep tissue damage to a minimum, the implants should be biocompatible and have diameters not much larger than 1 mm. Financial cost and mechanical strength are also important.

The three popular ferromagnetic elements, iron, nickel, and cobalt, have their respective Curie points at 770, 358 and 1130 °C, temperatures much too high for clinical hyperthermia. However, one can decrease the Curie point of any of these elements by mixing the proper amount of some other non-magnetic element into it, and numerous combinations with transition temperatures suitable for hyperthermia are discussed. After considering many of the potential candidates nickel-palladium and nickel-copper alloys have found to perform well and be relatively easy to manufacture

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