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HYPERTHERMIA TREATMENT PLANNING

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REPORT OF
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Contents

1. Introduction

Although hyperthermia was first employed as a treatment for malignant disease in the last century, it is only relatively recently that its mode of action and clinical application have been subjected to serious scientific scrutiny. From the early 1970's a wealth of biological data has been accumulated from many institutions with the intention of elucidating the mechanisms of hyperthermic cell killing and of identifying optimum combinations of this rediscovered modality with the conventional approaches primarily of radiotherapy and chemotherapy. Since the latter part of the last decade, as the potential clinical benefit of hyperthermia became more apparent, considerable effort has been devoted to the development of techniques which could be used for the production and monitoring of elevated temperatures within the cancer patient.

At the present time, many clinical institutions have embarked upon hyperthermia programs largely on the basis of the encouraging results which have accrued so far. It is slowly becoming clearer which anatomical sites can be effectively heated, the physiological and biochemical conditions which make tumours amenable to this form of therapy, and the combinations with radiotherapy and chemotherapy which are likely to meet with the greatest success.

In spite of the high current level of interest in hyperthermia, it remains the case that our knowledge of its modes of action, either alone or in combination, and our experience in its application are rudimentary. Although there is strong evidence of a therapeutic benefit of hyperthermia under some circumstances at least, a cursory study of the literature indicates minimal uniformity in its clinical application.

When, as is typical, hyperthermia is applied in combination with radiotherapy or chemotherapy, variables such as dose (from radiation or drugs), sequencing, time delays and fractionation are all likely to significantly influence outcome. These factors have been dealt with elsewhere[2,3] and are beyond the scope of this report.

However, even in the approach to the physical problems of the therapeutic elevation of temperature and its measurement, little consistency is to be found in the literature. In view of the variety of heating modalities currently in use and of the relative infancy of hyperthermia as a clinical tool this lack of consistency is perhaps not too surprising. In spite of this shortcoming the development of hyperthermia as a clinical modality has, to date, not been seriously impeded.

The situation in the future, however, is likely to be quite different. Smaller centres with fewer resources of both equipment and skilled personnel are entering the field in large numbers. Unless they are to adopt the inefficient approach of accumulating their own experience, published clinical results need to include sufficient information to permit duplication of general techniques even with equipment from different suppliers.

If hyperthermia is to be applied with maximum efficiency, criteria for the selection of the optimum heating and thermometric techniques need to be available. If the influence of variables such as radiation dose and fractionation is to be understood and optimized to the advantage of the patient, it is essential that the parameters describing the hyperthermia aspect of a treatment strategy be defined and controlled as tightly as possible.

This report is concerned with those parameters which describe the heating modality and its application to the patient. By analogy with conventional radiotherapy we wish to accumulate the relevant information to permit the decision making process known as treatment planning to take place. Due to the comlexity of the interaction between the non-ionizing radiation beams frequently used for heating and the inhomogeneous human body, and due to the unpredictable physiological response to temperature elevation, many significant decisions have to be made during the treatment. This contrasts with conventional radiotherapy in which the major technical decisions, in almost all cases, are made in the absence of the patient.

Conventional radiotherapy has now progressed to the stage where there is little room for ambiguity or error in a treatment plan. Definitions of the relevant treatment parameters are universally understood and accepted; standard treatment techniques have been established for many sites ; calculational techniques are sufficiently accurate under most, even complex conditions" ; concensus has been reached on which dosimetric parameters need to be measured and to what accuracy.

It should be the aim of the hyperthermia community to attain a similar degree of rigour and precision in the selection and specification of a hyperthermia treatment. Unfortunately, a major and fundamental difficulty is encountered at the outset of this endeavour. Whereas in radiotherapy the basic parameter used to specify the treatment - the dose - has a clear physical definition, this is not the case in hyperthermia. Of course, dose in radiotherapy cannot alone fully describe a course of treatment, neither can it in general be used to predict outcome. However, the identification and definition of this basic parameter has probably contributed more to the success of radiotherapy than any other development in its history with the possible exception of supervoltage machines. The specification of a comparable unit for use in hyperthermia has been the subject of study[8,9]. At the present, however, there is no consensus as to a unit of thermal dose of general applicability. This being the case it is necessary to proceed on the basis of the existing information which indicates clearly that biological damage is a function of both time of exposure and temperature. As the functional relationship between these two parameters and dose remains unclear, treatment description at this stage requires specification of the time course of the tissue temperature distribution.

Two further areas of distinction between hyperthermia and radiotherapy warrant brief discussion. Firstly, with the exception of brachytherapy techniques, it is the aim of conventional radiotherapy to achieve a uniform dose throughout the target volume. In the majority of cases the use of multi-portal supervoltage x-ray beams results in this objective being approximately met. In contrast, present hyperthermia technology, excluding whole body hyperthermia, yields very non uniform patterns of energy deposition. Furthermore, even if energy deposition were

uniform, physiological effects (blood flow) and differences in thermal properties such as thermal conductivity, among different tissues would result in generally very non uniform temperature distributions. In designing and implementing clinical thermometry it is important to appreciate the high degree of temperature non-uniformity which is present.

Secondly, prospective treatment planning which plays an essential role in conventional radiotherapy is of limited use in hyperthermia. For the majority of conventional radiation treatments it is considered unnecessary to confirm by in vivo measurement during treatment that the correct dose has been delivered.

Exceptions occur, of course, when vital radiosensitive organs are in close proximity to the radiation field. However, in general, specification of the radiation beams and calculational techniques are sufficiently advanced to permit the distribution of energy deposition, under given anatomical conditions, to be computed with high accuracy.

In contrast, the effect of hyperthermia depends not simply on energy absorbed per unit mass but in some, as yet undefined, way on the resultant temperature rise and its time course. The bioheat equation describes the dependence of temperature both on the energy absorption rate and on the rate of dissipation of energy. The former quantity is, in any event, more difficult to determine than in the case of ionizing radiation due to, for example, the complexity of the source field and reflections which can occur during radiofrequency, microwave and ultrasound heating. The major difficulty, however, is encountered in quantitating the heat loss mechanisms at play in the human body. Under conditions of steep temperature gradients, conduction is often the dominant mode of heat loss. The other contribution is, of course, blood flow and its significance for hyperthermia has been the subject of much study[12]. The presence of this latter unpredictable and time dependent heat transport mechanism has, as its consequence, one of the major practical differences between treatment in hyperthermia and that in conventional radiotherapy. In vivo measurement, whether by invasive or non-invasive means, will remain essential for each and every hyperthermia treatment.

The subject of this report, treatment planning for hypertyhermia, may be resolved into three components which are introduced below.

Specific Absorption Rate and its Distribution is the determination of the rate of energy absorption per unit mass, wkg^{-1}, in three dimensions under specified conditions in standard phantoms or in a patient from a given treatment machine.

The data accumulated during this procedure characterize the heating technique under the specific conditions employed and permit general identification of those sites and target volumes which are likely to prove amenable to treatment with a particular technique. In addition, the distribution of the Specific Absorption Rate [SAR] forms one group of input parameters which is essential for the calculation of the temperature distribution in vivo.

Temperature and its Distribution is the determination of the distribution of temperature in three dimensions in a patient throughout the course of a clinical treatment.

The temperature data accumulated during the clinical treatment form the most valuable record of that treatment and are the ultimate source of data characterizing the heating session. In practice, and with currently available invasive thermometry, complete temperature distributions in vivo cannot be determined. The state of the art is presently limited to recommending minimum procedures which could probably indicate when an appropriate hyperthermic treatment had been delivered". It remains a topic of considerable research interest to devise methods of deducing complete temperature distributions from the limited measurements possible in the clinic.

Treatment Planning is the selection of the optimal treatment technique and the geometrical configuration of that technique based on a knowledge of the performance of available treatment machines and on the computation of the expected three dimensional temperature distribution in a patient.

This definition describes closely the decision making process known as treatment planning in radiotherapy. The difference in practice between the two is that, in the case of hyperthermia, the computational aspects are less advanced and are subject to far greater uncertainty.

In the sections that follow each of the three areas defined above is discussed in some detail. After a brief review of the relevant recent literature on these topics suggestions are offered as to how the current state of knowledge may best be applied in the clinical environment taking into account the wide variation in the equipment available and its degree of sophistication. From the ensuing discussion, areas requiring further study can be identified.

2. Specific Absorption Rate and its Distribution

The aim of performing Specific Absorption Rate [SAR] measurements is to characterize the energy delivery equipment by determining the pattern of energy deposition. Although a variety of heating techniques is now available the only ones for which SAR has little or no meaning are whole body heating via conduction through the skin and/or the inhalation of hot gases[14] and regional methods employing extracorporeal heating of blood[15].

For some systems calculation may be a very appropriate approach to applicator design and characterization[16,17]. At the present time it is necessary in all cases, however, to confirm by judiciously chosen point SAR measurements under simple geometrical conditions in a phantom that the expected distribution is being produced. A further essential reason for performing some physical measurements of SAR is safety. The accuracy required here must provide sensitivity sufficient to identify the presence of unexpected hot spots which occur under some conditions'*.

2.1 The Source of Energy

If the SAR measurements to be made are to be assessed as being reasonable for the technique employed it is necessary to obtain a basic understanding of the operation of the applicator.

For external radiative electromagnetic and ultrasound techniques an important determinant of the depth of penetration in a specified semi-infinite medium (defined as that depth at which the intensity of a plane wave has dropped to e^{-2} of its initial value) of the unmodified therapeutic beam is the frequency. The frequency of operation of a system is easily established from the supplier's literature.

The presence of harmonic distortion is usually not a problem with radiative techniques although harmonics will decrease the penetration of both electromagnetic and ultrasound beams. The main restriction on the presence of harmonics will, in most cases, be government regulations covering the emission of electromagnetic energy. Depth of penetration which strictly applies only to plane waves, has no meaning for the other methods of induction of hyperthermia and has little revelance to interstitial microwave techniques in which the radial intensity decrease and coherence effects largely determine the SAR pattern. However being the fundamental operating parameter of a system the frequency, and its range where applicable, should be known.

An additional descriptor of radiative electromagnetic methods is the mode of antenna excitation. The mode of excitation contains much information on the three dimensional field distribution" and can be used to suggest the most informative series of phantom measurements.

The physical size of an applicator, in addition to influencing the penetration of the heating beam[19,20] places constraints on the largest area perpendicular to the axis of propagation which can be heated. External microwave applicators will effectively heat areas which are significantly smaller than the area of the radiating antenna. An ultrasound beam will not spread to cover an area larger than that of the transducer aperture before the intensity drops below the therapeutic level. In contrast capacitive and inductive approaches may heat areas which extend beyond the boundaries of the applicators. However, applicator size remains a constraint on the largest area which can be heated.

Experience with regional techniques in which a thick transaxial section of the patient is exposed to significant electromagnetic fields [e.g. B.S.D. Annular Phased Array System[23] and the Magnetrode[22]] is limited. Calculation supported by comprehensive in vitro and in vivo measurement is essential[23] if the true extent of the heating field is to be discovered.

Whilst a knowledge of the physical dimensions of an applicator and its mode of excitation can be useful in the design of phantoms for studying SAR distributions it is important to base treatment planning decisions on more detailed experimental studies possibly supplemented by calculation. Generally tissue to be irradiated is in the near field of a microwave applicator and thus the electromagnetic field, which may have non-radiative components, does not behave like a plane wave. under such circumstances the depth of penetration corresponding to the operating frequency can be used as a rough guide only. Ultrasound transducers are frequently focussed to improve the effective penetration of the beam, but even so the target tissue is usually in the near field[24].

However, in spite of these complications familiarity with the heating technique is the first step in the treatment planning process. Construction of appropriate phantoms, selection of measurement sites and preliminary decisions on the anatomical regions which may be successfully heated can all be based on knowledge and understanding of the heating technique.

2.2 The relative SAR distribution

The relative SAR distribution is necessary for the input to the calculation of the temperature fields produced during a clinical treatment and thus is an essential element of the treatment planning process. Under some conditions calculation may be the-source of the most comprehensive information on SAP distribution[16,25] but in ail cases experimental determination of the overall pattern should be obtained. If the density and specific heat of heated tissue are known it is possible to deduce limited SAR values from in vivo measurements. However, in general, static phantoms are preferred as their properties are known, geometry can be standardized and a greater number of measurement sites is possible.

In recent years phantom materials have been developed which correctlv mimic the electrical and acoustic properties of tissues such as muscle and fat over a wide range of frequencies[26,27,28]. As the intended use of these materials is to study the distribution of energy absorption, their thermal properties are not necessarily the same as those of tissue and can be considerably different from living tissue in which blood flow is often the most significant heat loss mechanism. However, their thermal properties are in general known to sufficient accuracy to permit extraction of SAR values from measurements of rates of rise of temperature.

To avoid convective effects electromagnetic heating modalities are usually studied in solid or semi-solid phantoms. More complete distributions, particularly from ultrasound applicators, may be obtained from liquid phantoms in which a transducer is scanned and the relative intensity pattern obtained".

The information obtained from phantom studies is easier to evaluate or to compare with that expected from the applicator employed when the measurements are made in a homogenous material with a flat surface. As the intention is to obtain SAR distributions and not to attempt to simulate the final temperature distribution in vivo the correct thermal properties of the phantom material are not essential. Blood flow can to some extent be simulated through the design of dynamic phantoms. The role of such devices, however, remains unclear at the moment: certainly, they are not relevant to SAR studies.

The presence of electrical or acoustic inhomogeneities can perturb the SAR distribution to a significant degree and must therefore receive consideration. Clearly it is not possible to simulate all anatomical configurations that might be encountered. However one or two representative cases can provide valuable additional information on the characteristics of a particular heating technique[18]. The majority of investigations aimed at characterizing applicators will rely on measurements of rates of rise of temperature in solid or semi-solid phantoms at the commencement of heating before conduction becomes significant. The behaviour of the thermometry system used to make these measurements requires some discussion.

There are two approaches in widespread use. Thermography has proved extremely valuable in assessing quickly the temperature distribution through a plane of a phantom. With a temperature resolution of approximately 0.2°C and a spatial resolution of 3mm thermography with split phantoms is capable, with proper care, of quickly producing two dimensional temperature distributions of an accuracy that is adequate for many purposes. When thermography is employed it is essential that the phantom be heated rapidly so that the presence of conduction does not significantly influence the temperature distribution. In addition, thermographic examination of the split phantom must promptly follow heating if distortion of the temperature pattern, due to heat loss from the phantom surface is to be avoided. As has been pointed out previously[31] it is likely that the heating system will have to be operated at or near maximum output to obtain the greatest accuracy. A major advantage of thermography is the ease with which unexpected hot or cold spots may be identified in phantom studies. These may be due to the properties of the applicator-phantom combination or the presence of perturbing thermometers.

When thermographic equipment is neither appropriate nor available resort must be made to point measurements using invasive thermometers. It is common practice when employing this approach to incorporate into the phantom an array of tubes through which thermometers can be inserted[33]. Clearly the number of sites at which measurements can be made is restricted. However, interpolation between measurement points can yield the appropriate degree of accuracy in those situations in which the SAR is changing only slowly with position.

Point SAR measurements using invasive thermometry are clearly more prone to error when fields of high SAR gradient are involved. Examples of these would be the SAR distributions from interstitial antennae and those produced by ultrasonic transducers. In the former case the most accurate method may be calculation with the gross features of the distribution confirmed by thermographic examination[33]. In the latter, intensity plotting in a liquid phantom using an ultrasonic transducer yields information of an adequate spatial accuracy" although measurements in a tissue equivalent U.S. phantom may be preferred.

In those cases in which point temperature measurements are made in solid or semi-solid phantoms care must be taken to ensure that measurement artifacts do not compromise the accuracy of the determination". Thermal insulation of the sensor can lead to error due to the time delay before the rate of rise of sensor temperature equals that in the phantom[37]. In the presence of high temperature gradients, e.g., with interstitial techniques, conduction along the probe can lead to significant error[38,39]. In the case of ultrasound irradiation the presence of plastics surrounding the thermometer has been shown to yield artefactual readings[40]

In view of the above discussion the following guidelines can be offered for the characterization of heating modalities through relative SAR distributions. Where calculations are considered to be a reliable guide, at least in homogenous tissue, these should be available. Where calculations are not considered helpful experimental measurements should be undertaken and these in any case should be used to confirm the gross features of a calculated distribution. Phantoms for such studies of applicators for local heating may be constructed according to established recipes and procedures[27] and, to avoid edge effects, should be at least three depths of penetration deep and possess a surface area three times that of the applicator. Impedance matching procedures, where applicable, should be employed although active surface cooling should not. The accuracy and sensitivity of the temperature monitoring procedure should be sufficient to determine SAR values to within 10% and with a spatial accuracy of 3mm at least in the regions in which the SAR exceeds 50% of its maximum value. In general, with electromagnetic heating it will be reasonably straight forward to attain the required degree of accuracy at sufficient depth in homogenous material. Close to the surface of the phantom the discontinuity in both thermal and electrical properties could lead to substantial error and, for this reason, it is suggested that normalization be made to the point at 1 cm depth on the central axis of the beam. Errors at points proximal to this may well exceed the 10% value given above.

In the strong gradients associated with interstitial techniques it is unlikely that point measurement can yield the required degree of accuracy. However, calculations for these situations have received considerable attention and these may form the main source of information on relative SAR distributions".

Intensity measurements on ultrasonic applicators should be capable of reaching the degree of accuracy specified above with appropriate techniques in an appropriate liquid phantom.

Regional techniques in which a transaxial section of a patient is heated require a somewhat different approach. To maintain simplicity the phantom for these studies should be of circular-or elliptical section and; of a length sufficient that at its ends the SAR has dropped to 10% relative to its maximum value. In selecting a phantom for this application the significance of possible resonant effects should be recognized.

Electromagnetic and ultrasonic coupling materials should be used if they are to be employed clinically. They should be applied using a standard, and reproducible and specified method.

Consideration should be given to extracting the required amount of information in the minimum time and here knowledge of the electromagnetic or acoustic field patterns is valuable. Many techniques such as capacitive and inductive radiofrequency heating and stationary ultrasonic insonation produce fields in homogeneous and symmetrical media that have been shown to have cylindrical symmetry. In such cases an SAR distribution in one plane containing the axis of symmetry of the applicator may be sufficient. More complex electromagnetic field patterns will, of course, require more comprehensive investigation.

A straightforward and useful approach to summarizing SAR data so obtained has been suggested. The useful thermal field size has been defined as the area enclosed by the iso SAR curve corresponding to 50% of the maximum SAR at the appropriate depth. For external radiative, capacitive and pancake single coil inductive devices specification of the useful thermal field size could be made at a depth of 1cm. Therapeutic ultrasound fields

often exhibit significant intensity fluctuations both axially and laterally and hence their characteristics require more complete measurement than is generally needed for electromagnetic fields. An appropriate approach might be to specify, at a depth of 1 cm, the size of the field as defined by the locations at which the lateral edges of the outer peaks have fallen to 50% of their maximum values.

Whilst the concept of useful thermal field size is convenient for applicator characterization and quality control it is understood that it is not necessarily or in general coincident with the therapeutically relevant field size.

The value of such a simple descriptor for techniques such as the Annular Phased Array System or the Magnetrode is more questionable. In these cases it is necessary, under some standard conditions to identify the location of the maximum SAR and define, in the plane containing the coil or antennae, the area enclosed by the 50% SAR If the position of maximum is on the surface it is recommended that normalization takes place with respect to a point 1cm deep to avoid the difficulties of measurement at the surface.

For external applicators the thermotherapeutic penetration depth[43] is a further quantity which aids the specification of the heating system. This is defined as the depth at which the central axis SAR falls to one third of its value at the surface. This figure gives an indication of the depth at which therapeutic heating is possible when irradiating plane, homogenous, muscle-like tissue with some surface temperature control.

Finally, representative measurements should be made with inhomogeneities present. Plane slabs simulating fat[27,44] of thicknesses 5 and 10mm will suffice in most cases to identify possible hot and cold spots.

The information collected by the above means is the minimum necessary as the input to the treatment planning process. In addition, the data so collected will be valuable for the comparative assessment of techniques within and between centers.

2.3 Absolute Specific Absorption Rate

Absolute Specific Absorption Rates measured under experimental conditions are far less important in hyperthermia than the analogous dose rate is in conventional radiation therapy. Temperature, one of the quantities which is known to strongly influence biological effect, is dependent not only on the rate of energy absorption and specific heat but also on the largely unpredictable local energy transfer mechanisms.

However, the relationship between absolute Specific Absorption Rate under some standard conditions and manufacturer supplied power indicators is an essential characteristic of the equipment and should be determined. Assisted by calculation and the relative SAR distribution this quantity will help to indicate the maximum blood flow for which therapeutic temperature rises can be achieved. It can also be used to indicate the amount of surface cooling which must be employed to limit the temperature rise at the skin.

The most important potential use of absolute SAR is for input into calculations of temperature distributions. Provided applicator - patient geometry is consistent from treatment to treatment, i.e., electrical or acoustic impedance matching is reproducible, knowledge of the absolute SAR at a given point removes one variable in the calculation of the temperature distribution.

Absolute Specific Absorption Rate values should be measured at a point 10mm deep [to avoid surface effects] in a standard specified phantom material and at the radial location of highest SAR. This will usually be on the central axis for a microwave or ultrasound device. Dividing the SAR by the net power applied yields the applicator heating efficiency[13]. For a capacitive heating system both the relative SAR distribution and its absolute value at any point depend on the separation of the electrodes and on the materials between them. These parameters should be specified when reporting results.

For interstitial microwave techniques, in which the reduction in SAR with distance is rapid, the thermometer used should be positioned 5mm from the central axis of the conductor and at the level of the most proximal break in the outer conductor. Localized current field techniques require a standardized spacing of the electrodes if reproducibility is to be achieved. An appropriate spacing is 10mm with the absolute SAR being measured mid-way between two electrodes.

Regional approachcs such is the APAS and the Magnetrode are somewhat more difficult to handle. Whilst the Magnetrode produces zero SAR on its axis this is not the case with the APAS. For these devices absolute SAR should be determined at a location close to its maximum value in a standard phantom and under standard conditions of geometry and machine settings, such as phase in the case of APAS.

Perhaps the greatest value of the applicator heating efficiency is that it facilitates inter-institution comparisons of heating techniques. At the present with a wide variety of commercial and custom-built equipment in use there exists considerable difficulty in identifying comparable treatments in different centers. Availability of a quantity which permits comparison even under rather simple geometrical conditions will be of value when collating and examining data collected from different institutions or different modalities in the same institution.

2.4 Coupling and Matching Devices

Coupling and matching devices are frequently employed with external heating techniques. Frequently such devices also serve to limit the temperature rise at the patient's skin. If a hyperthermia technique is to be adequately characterized it is important that this feature of the equipment be understood.

At radiofrequencies with both the capacitive and inductive approaches, the impedance seen by the generator can be altered to maximize the power transfer to the tissue of interest. It is appropriate to identify the range of conditions under which efficient power transfer can take place. The applicator heating efficiency

[defined in Section 2.3] should be measured for representative separations of the capacitor plate or coil from the muscle equivalent phantom. Of particular importance is the effect of fat between the applicator and the muscle like tissue which is to be heated. The influence on the applicator heating efficiency of a l0mm thick fat layer can be assessed by comparing the heating efficiencies with and without simulated fat in position under the configuration that optimizes power transfer in the absence of fat.

Similar studies are required for external microwave applicators where the presence of fat can influence the coupling efficiency.

It should also be noted that the area of the useful thermal field (Section 2.2) can be influenced and in some cases determined by the coupling arrangement. Saline filled bags used with capacitive techniques significantly influence, through their size and conductivity, the heating field. Similarly it is known that bags filled with non-conducting de-ionized water, often used to couple waveguides to patients, can influence both the applicator heating efficiency, which they are intended to maximize, and the SAR distribution". In designing experiments to investigate the influence of fat like tissue on the applicator heating efficiency it should be recognized that the presence of fat will itself alter the SAR distribution. For consistency and to avoid the steep SAR gradients at the fat-muscle interface it is recommended that the reference point for such measurements be 10 mm deep in the muscle like tissue.

If such devices are to be employed clinically it is important that they be assessed under conditions that represent those likely to be encountered during patient treatment. The variability in coupling and its influence on both absolute and relative SAR will form one limit on the accuracy with which calculated temperature distributions can be obtained.

3. Temperature and its Distribution

The potential success of a planned hyperthermia treatment can be gauged from a knowledge of the properties of the heating modality employed and the anatomy and physiology of the patient in the region of the target. The actual success of a hyperthermia treatment, in the sense of achieving and maintaining a desired temperature distribution, cannot be assured solely on the basis of prior measurement whether in the laboratory or clinic. It is certainly the case now and likely to remain so for the foreseeable future that in vivo temperature measurements will be required during each and every treatment.

Two approaches to thermometry may be identified. The first is invasive thermometry in which temperature measurements are made at specific and predetermined points within the heated region. The number of measurement sites for this approach is clearly limited by practical considerations. The alternative of non-invasive methods, which in principle are capable of yielding three dimensional temperature maps, have considerable appeal for hyperthermia applications. Although many such techniques have been investigated none has yet been identified which combines the necessary spatial and temperature resolution over clinically relevant volumes.

Invasive thermometers are the only devices so far which have demonstrated clinical utility and the ensuing discussion is therefore devoted to these.

3.1 Thermometer Description

In assessing the suitability of a particular technique for a particular heating modality it is necessary that the underlying physical principles of operation be understood. Only with such information is it possible to evaluate the extent of compatability with the heating technique and the anatomical region of interest. Thorough reviews of thermometers for hyperthermia have been given elsewhere[36,50] and only a few of their major characteristics will be re-iterated here.

Thermocouples remain popular devices for measuring temperature in the clinical environment with over 60% of reported studies having relied on their use for temperature measurement. They offer the advantages of cost, ease of fabrication, size, adequate accuracy, stability and multisensor capability. The major drawback of thermocouples has long been recognized as their interaction with the strong electromagnetic fields employed frequently in clinical hyperthermia[52,53]. In addition they suffer from from thermal smearing due to heat conduction in their metallic leads and, depending on their coating and packaging are known to interact with ultrasonic fields[40]. Sources of error including interaction effects must be understood and appreciated and are dicussed in Section 3.3 below.

Thermistors are extremely sensitive devices and, when connected to the measurement electronics through high resistance leads, will neither perturb nor be perturbed by electromagnetic fields. Currently, multisensor probes of a size acceptable for clinical use have not been fabricated and thus to extract the maximum information from an insertion resort must be made to tracking techniques[55,56]. The remaining two clinically applicable techniques both involve temperature dependent optical properties of crystals which are remotely sensed through non-conducting optic fibres[57,58,59]. Interaction between such thermometers and electromagnetic fields is not measurable and these devices are usually described as minimally perturbing. Manufacturer's literature can be consulted to identify the smallest catheter into which the sensor will fit. Susceptibility to humidity and the method of sterilization to be used are general properties of thermometer systems which should be known before embarking on clinical treatments. As measurement during treatment is vital in clinical hyperthermia, the gross features of the thermometry system must be identified and appreciated at the treatment planning stage. Armed with such knowledge wiser choices of thermometer location and measurement technique will be made.

3.2 Intrinsic Characteristics of the Thermometer

Both during the stage of planning a hyperthermia treatment and reporting the results of a clinical study, awareness of the intrinsic characteristics of the thermometry system is valuable. It is well known that the biological response of tissue to hyperthermia is a strong function of temperature and from this perspective high accuracy of the thermometry system is required.

It is recommended that thermometry systems for clinical use during local or regional hyperthermia be calibrated to an accuracy of 0.2°C with a precision of 0.l°C. Precision is defined in its usual way to reflect the reproducibility of measurement by one themometer or the agreement among different thermometers belonging to one thermometry system. These criteria are easily met by most available thermometry systems in the absence of artefacts (Section 3.3). In the special case of whole body hyperthermia highly accurate temperature contol is vital if serious side effects of the treatment are to be avoided. In this situation, which is accompanied by a fairly homogeneous temperature distribution, an accuracy of 0.05° C is recommended.

It should be noted that a temperature accuracy of 0.2°C implies effective thermal contact with the tissue being monitored. There are two conditions under which this can be difficult. Under some circumstances, which should be clearly identified during the treatment planning process, precise control of the surface temperature may be necessary. To merely ensure that the surface does not rise above some predetermined level may be inappropriate. In such cases it will be necessary to ensure that the temperature sensor accurately reflects the surface temperature and not that of any cooling technique applied.

The second situation in which poor thermal contact can impair temperature accuracy arises when temperatures are changing rapidly[37]. Pull treatment planning requires consideration of intended rates of

rise of tissue temperature and particularly for slowly increasing temperatures the 'thermal dose' accummulated during this phase of the treatment can be significant. However, for rapidly rising temperatures the time constant of the probe, which is determined largely by the properties of its thermal insulation, could lead to temperature measurement errors and possibly even a safety hazard due to excessive hot spots not being detected rapidly. An appropriate sampling and display rate will also, of course, be necessary if a short probe rime constant is to be exploited.

The sensitivity of themometry systems in routine clinical use is typically 0.l°C, which is adequate for most purposes. The only situation in which greater sensitivity may be required is during attempts to quantitate blood flow [or effective thermal conductivity] using thermal washout following the interruption of heating[11,60].

The final intrinsic property of a thermometry system which should be considered is stabilitv. The frequency of calibration is chosen such that, with the known stability of a system, the precision and accuracy recommendations outlined above are not exceeded. Systems whose stability, when measured under the mechanical stresses experienced during clinical treatment, is so poor that these levels cannot be maintained during a single heating session are not appropriate for clinical use.

3.3 Sources of Error in Temperature Measurement

With the recognition both that in vivo temperature measurement is a vital component of clinical hyperthermia and that relatively high accuracy is required due to the rapid dependence of biological effects on temperature, considerable effort has been invested in studies of possible sources of error. As these errors impact upon clinical procedures and hence should be considered during the planning of a treatment they are discussed in this document. Interference with the sensitive electronics

which conditions and records the signals from the temperature sensor has been a long recognized difficulty of making measurements in the presence of strong electromagnetic heating fields. Techniques for minimizing the consequences of electromagnetic interference have been discussed" and many thermometry systems have been designed with shielding and filtering configurations aimed at the elimination of this problem[62]. The presence of interference can be identified by laboratory experimentation" or in the clinic by the very rapid change in indicated temperature which accompanies changes in applied power[51]. If, such an effect is present it must be regarded as a systematic error and steps taken to eliminate it altogether[64]. In those cases in which elimination is not possible this effect can be handled by making measurements during brief [<1 sec] interruptions of power. At the planning stage the frequency of measurement and hence of power interruption must be decided. To avoid overshooting the target temperature by more than 0.5°C, measurements will need to be made at times which correspond to this temperature change during the initial phases of heating. Once the plateau temperature has been attained clinical experience will dictate an appropriate frequency of measurement although 1 per minute would seem to be suitable and easily achievable in most cases.

In addition to interference effects metallic thermometers, as are commonly used, are afflicted by problems associated with their self heating. The magnitude of the effect under one particular-set of experimental conditions has been quantified"' and its significance for the equilibrium temperature distribution assessed[65]. A study of techniques for dealing with self heating errors has concluded that the effect on the sensor itself may be effectively eliminated by making measurements during power interruption[66]. However, the period after cessation of heating before a reliable measurement can be made is considerably longer than that required to eliminate interference effects being several probe time constants which could be as long as 5-10 sec. This same study[66] failed to identify a method for

effectively dealing with the perturbation of the temperature distribution due to an artefactual heat source within the tissue. Should a thermometer under clinical conditions exhibit a degree of self heating which is likely to significantly perturb the temperature distribution it is inappropriate for a hyperthermia application.

If a small to moderate degree of self heating is known to occur [which is insufficient to perturb the tissue temperature by more than 0.1°C] it can be dealt with by a power interruption of adequate duration. The decision on whether or not to employ such a technique and how to employ it must be made at the treatment planning stage and based on the known or expected characteristics of the thermometer. Other effects have been identified during the use of both thermocouples[67] and diodes[68] and the significance of such artefacts for clinical hyperthermia should clearly be assessed.

A further effect which can be significant when the temperature sensor assembly is thermally conducting is smearing or distortion of the temperature distribution due to conduction along the sensor. Such an effect is clearly more significant in high temperature gradients such as are found frequently in interstitial applications; close to large blood vessels; in the penumbra of the heating field and near the surface. At the planning stage some estimate of the expected magnitude of the effect should be made[36,38,69]. If the error exceeds or is likely to exceed that stipulated in Section 3.2 an appropriate correction will be required.

Thermal lag due to the insulating properties of the catheter within which the temperature sensor is located can, under certain conditions, influence clinical procedures. If a tracking technique is employed to maximize the temperature information obtained per insertion[55,56] sufficient time must be allowed at each location for thermal equilibrium to be attained. This time will depend on the time constant of the sensor within its encapsulation[37]. Similarly

if it is intended to determine the SAR at certain locations in vivo by observing the rate of change of temperature, accommodation must be made for time constant effects".

An additional problem has been identified when performing temperature measurements in ultrasonic fields. The interaction of the field with plastic catheters has been observed[36,40,70,71] and clearly the selection of a thermometry system for use under these conditions must acknowledge the existence of this effect.

Familiarity with the behaviour of the particular thermometer available is essential if temperature information obtained during clinical hyperthermia is to be a valid and meaningful record of the treatment.

3.4 Thermometer positioning

The aim of thermometry in hyperthermia is, by measurement or calculation or by a combination of the two, to determine the distribution of temperature [and its time course] in three dimensions. Particularly in view of the marked lack of homogeneity of temperature achievable with almost all heating modalities, position accuracy is of vital importance. In Section 4 of this report recommendations concerning the locations of thermometers during clinical hyperthermia are given. In this section general considerations concerning thermometer positioning are discussed,

With the exception of whole body hyperthermia, temperature gradients of between 1 and 10°C cm^{-1} are characteristic of current clinical hyperthermia heating technology. The lower value is achievable with regional heating techniques while higher values are typical of gradients encountered during the application of interstitial techniques, near the surface of externally heated sites and, in general, near tumour/normal tissue boundaries[60]. The reproducibility of set up from treatment to treatment should ideally be 2mm at least where position with respect to both patient anatomy and applicator must be

considered. It is recognized however that this level of precision may, under clinical conditions, be difficult to reach.

In the absence of other constraints it is clear that thermometry will be more reproducible if the locations of measurement are in regions where large temperature gradients are not expected. Unless there are good reasons, which will be considered during the treatment planning process, measurement sites close to electrical or thermal discontinuities should not be used to control the treatment. Large blood vessels which could constitute significant heat sinks[69] may require special consideration if they lie within the intended therapeutic volume of the heating field.

The use of linear arrays of sensors is a convenient technique for increasing the temperature information which can be obtained from the insertion of one catheter. An alternative method which employs only one thermometer to reach the same objective is a linear tracking technique[55]. In view of the recommended precision of positioning it is unlikely to be appropriate to routinely make temperature measurements at locations closer together than about 5mm. Exceptions to this may be unavoidable if critical regions of the patient coincide with steep temperature gradients and in such cases precautions will be necessary[38].

In addition to considering the precision of location of temperature measurement, accuracy should also be of concern. Characteristics of the thermometry technique which can lead to systematic errors in the identification of the location of measurement must be recognized and appropriate allowances made. Several investigations of sources of this type of error have been made[38,67]. It appears that with thermally conducting probes, conduction along the probe can have a significant influence which increases as the temperature gradient increases.

Finally, a technique for identifying the locations of temperature measurement relative to the patient's anatomy and the applicator position must be selected before clinical studies commence. The specification of a temperature achieved during clinical hyperthermia without a clear and accurate description of the location of the measurement is of limited value. Unfortunately, many published reports reflect this shortcoming. Several techniques are available for identifying the location of a temperature measurement. Computed tomography in the presence of radio--opaque skin markers to indicate applicator position is universally applicable when available. Stereo or orthogonal x-ray films taken with the probe catheter filled with a radio opaque substance can be employed to identify the position in three dimensions of the catheter. Techniques and computer programs designed for use with radiation brachytherapy are well known and available. Tomographic techniques such as ultrasound and MRI can also be used to help identify catheter location.

Bearing in mind that catheters used to contain clinical thermometers have diameters which usually are not less than 1mm, a realistic spatial accuracy for clinical hyperthermia is 2mm. The techniques mentioned above are generally capable of identifying catheter location with respect to patient anatomy to this degree of accuracy.

3.5 Control circuits, display and recording

With the advance of technology, increasingly sophisticated methods are available for the real time manipulation, display and recording of the large amount of temperature data accummulated during a clinical hyperthermia session. It is clearly an important aspect of the planning of a treatment to decide:

a) which and how much temperature data will be recorded?

b) at what time intervals?

c) which signals will be used to determine the course of treatment? and

d) will automatic feedback control be employed?

The use of microprocessor controlled thermometry which probably contribute to the majority of current clinical treatments allows considerable flexibility in the application of real time thermometry. High capacity storage devices offer the added advantage of the possibility of detailed retrospective analyses of a heating session and the value of this facility will be discussed in the next section. Here the features of contemporary thermometry systems which are likely to be of greatest value to hyperthermia dosimetry are considered in general terms.

Multichannel thermometry is now regarded as essential due to the inhomogeneous nature of the temperature field produced during clinical hyperthermia. The large amount of data yielded by such an approach brings with it the problem of how to present information to the operator in an easily digestible form. One difficulty commonly encountered is correlating the various temperature channels, which are usually identified by numbers, with their positions in a patient and hence their relative importance in determining the course of treatment. It is mandatory that a diagram of relevant patient anatomy and the probe catheters be available at each treatment to facilitate interpretation of the data presented.

Digital displays of individual temperature channels are, in the absence of other information. difficult to interpret as a treatment is being assessed in the clinic. A bar graph presentation is of somewhat more value as some idea of the temperature distribution may be gleaned more easily. Possibly the most informative display for the operator controlling the treatment is a graph showing the time course of each temperature channel. It is not uncommon for patient movement or some other factor to necessitate readjustment of the applicator position during treatment. A visual representation of the treatment before and after such an adjustment greatly aids the rapid optimization of set up.

Two additional operating characteristics of thermometry systems warrant brief discussion. The first is the frequency with which each temperature channel is read and the presented data updated. With typical

temporal temperature gradients of 1°C min^{-1} a read frequency of 10 min^{-1} for each channel is consistent with the recommended measurement accuracy. The second is the frequency of storage of temperature data on disk or tape for later analysis. Under most conditions storage of data at 1 min intervals will provide sufficient information to characterize the behaviour of temperature at each measurement site. Circumstances under which a more frequent storage of temperature information will be necessary are special investigations such as the quantitation of blood flow through thermal clearance techniques or the determination of SAR in vivo by examining the initial rate of rise of tissue temperature.

The final consideration to be reviewed at the time of planning a hyperthermia treatment is automatic control of the power output of the heating device based on incoming temperature information. Technically this approach is straightforward but it requires a high level of confidence in the selected clinical technique and control temperature point(s) if it is to be implemented. Hyperthermia is still at the stage where operator and attending physician competence and experience are vital ingredients for a successful hyperthermia program and, with very few exceptions, it seems unlikely that control of a clinical treatment session will be delegated to a machine in the foreseeable future.

This section of the report has addressed in general terms the accummulation of temperature data during a clinical treatment. With present invasive thermometry the information obtained in this way will clearly be spatially incomplete. Methods by which this shortcoming may be remedied will be among the topics to be discussed under the heading of Treatment Planning.

3.6 Surface Cooling

Although a surface cooling facility need not in general influence the SAR distribution it frequently serves the additional function of an electric or acoustic impedance matching device (Section 2.4). In any event its capability will need to be appreciated if effective treatment planning is to undertaken.

Forced air systems are relatively easy to implement when external microwave or radiofrequency techniques are employed. With the flow of air parallel to the patient surface cooling may be uneven if the surface anatomy is irregular and this effect should be recognized. Air flow through the applicator and therefore normal to the surface may be more appropriate than parallel flow and should be designed such that the air flow is greatest where the power density is greatest.

Water, whether de-ionized or containing sodium chloride, flowing through a flexible "bolus" between the applicator and the patient is probably the most commonly used means of limiting the rise of skin and near surface temperature.

With such devices it is necessary to appreciate that the efficiency of heat removal from the skin depends on the thermal contact berween the surface and the cooling liquid[48]. Under conditions of uneven surface, contact may be poor in places resulting in relatively high and unpredictable temperatures.

4. Treatment Planning

Treatment planning, whilst clearly an essential aspect of clinical hyperthermia, is fraught with difficulty. Certainly the confidence placed in radiotherapy treatment plans can not be justified in the case of hyperthermia. However, recent years have seen considerable activity in this area resulting in the development of philosophies and techniques. In what follows different paths by which treatment planning for hyperthermia may be approached are suggested. Various degrees of sophistication can be employed along these paths and in general the limitation on sophistication will be imposed by limitations of resources. The four approaches described below follow the original suggestion by Cetas and Roemer[72] with their classification given in parentheses for Sections 4.2 to 4.5.

4.1 Identification and description of the target volume and adjacent tissues

The obvious first step in any attack on localized disease is the identification of the target. It is widely recognized that the precision with which this can be carried out in the case of malignant disease is in general poor. Generous margins around identifiable disease are employed whenever possible to account for microscopic spread. It is also noted that the limitation on target volume for conventional radiotherapy is frequently imposed by the proximity of adjacent normal and radiosensitive tissues. In spite of these difficulties it is essential to employ the most precise and sensitive techniques available to achieve this first step in the treatment planning process.

The most appropriate and convenient currently available technique for localization of the tumour and display of adjacent anatomy is X-ray transmission computed tomography [CT]. Multiple consecutive slices contain probably the most complete and spatially precise information available for any anatomical location. For certain lesions ultrasonic scanning can be a satisfactory technique. Visual inspection and palpation can serve to identify the circumference of many superficial tumors such as chest wall recurrences although precise information concerning the depth of invasion will be lacking. Plane film X-radiography is routinely employed for localization for conventional radiotherapy and, although it can fulfill a similar role for hyperthermia, it is inferior to CT in both applications. The contribution of Magnetic Resonance Imaging to target localization for hyperthermia is, at this time, unclear.

As in conventional radiotherapy, treatment planning for hyperthermia requires as its first step a series of patient contours with the target volume indicated. CT is the most appropriate source of this information and ideally it should be available in parallel contiguous planes.

An important point to note at the treatment planning stage is the need to record accurately the locations of thermometers used during the clinical application of hyperthermia. In many studies to date only the vaguest information is available concerning thermometer position and this shortcoming certainly hampers attempts to compare

data not only from different centers but also from the same center. The representation of patient anatomy and target data in the form of contours should allow for the entry of thermometer position at a later time.

In addition to the spatial resolution available with X-ray computed tomography a further reason for employing this imaging modality is its ability to discriminate clearly between different tissues and hence identify electric or acoustic inhomogeneities. Very few centers can currently handle such information accurately with the aim of deducing Specific Absorption Rate distributions. However the behaviour of electromagnetic and ultrasonic radiation in different tissues is qualitatively understood[49,73,74] and therefore the presence rparticularly of adipose tissue, bone and air cavities should be shown on the patient contour.

Thermal inhomogeneities are also obviously of considerable significance for clinical hyperthermia and these must be indicated on the patient contour. Of particular significance in this category is the presence of large blood vessels which have been shown to significantly influence the temperature distribution in their neighbourhoods[69]. Ideally the blood flow distribution in and out of the plane of the plan should be known and not just the sites of gross differences. At the moment it is possible to do little more than infer from anatomical data the likely degree of non-uniformity of flow within the heating field, however, the development of thermal washout techniques"" hold promise for the future.

Currently the majority of hyperthermia treatments are performed in conjunction with radiotherapy. The dose distribution from interstitial or external sources of ionising radiation can be calculated with high accuracy in almost all cases and both treatment planning and retrospective evaluation of clinical studies clearly require details of the radiation dose distribution. A vital component of treatment documentation is the record of adjuvant therapy and in the case of radiotherapy this record must include details of the dose distribution with respect to the actual patient anatomy.

In summary, treatment planning for hyperthermia requires, as it does for radiotherapy, an identified target volume superimposed upon the actual patient's anatomy. Such data in a quantity [ie. number of planes] which are sufficient to describe the geometry of the heated region to acceptable accuracy are essential as the first step of the planning process. Few centers are capable of even estimating SAR distributions from maps of electrical or acoustic tissue properties; however, such information should be indicated where possible on the patient contour. Evidence of non-uniform blood perfusion should likewise be indicated as significant temperature non-uniformity may well be present as a result.

4.2 General considerations of heating modalities (Comparative thermal dosimetry)

Comparative thermal dosimetry for use in treatment planning describes the process of selecting the most appropriate heating technique and applicator for a particular application. This process does not depend upon detailed accurate predicted temperature distributions but rather on matching available heating techniques to the target through a knowledge of the behaviour of the heating modality.

Targets may be grossly classified for this purpose into superficial [distal surface within 4 cm of the skin] and deep [all other sites]. Most of the clinical data accumulated to the present time has been gained from the treatment of superficial sites and the techniques for producing a therapeutic temperature rise under such conditions have been extensively studied. The most popular approach remains microwave heating using frequences which range up to 2450 MHz. Additional "external" techniqes include ultrasonic irradiation[75], capacitive heating[76] and inductive heating[77] although the latter, due to its toroidal heating pattern, is not straightforward to implement for most superficial sites.

The heating of deep seated tumours remains problematical. Several techniques have been developed which, theoretically at least, could be expected to produce therapeutic elevation of temperature deep in the body. These include inductive heating'"" ultrasonic irradiation" and the use of constructive interference of

electromagnetic waves[81]. It may be concluded that, at this stage, such techniques of heating deep seated tumours are still very much experimental and should not be undertaken in those centres which lack the physics, engineering and medical support for their safe implementation.

An approach to clinical hyperthermia which has found many followers in recent years and which may be applied to both superficial and deep seated tumours is interstitial hyperthermia. Clearly surgical intervention of a complexity depending on site is necessary if this approach is to be adopted. However, as with interstitial radiotherapy techniques the treated volume is localized and, with effective treatment planning, neighbouring normal tissues may be spared damage.

The first stage in comparative treatment planning is to ensure that the target in three dimensions is adequately covered by the proposed heating technique. Such a comparison will initially be undertaken assuming homogeneity of electric [or acoustic] and thermophysical properties.

The next stage is, through a knowledge of the physical behaviour of the heating beam in heterogeneous structures, to consider the likely impact of local anatomy on the SAR distribution. An extreme example of this process is the virtual impossiblility of employing ultrasound to heat regions with overlying air or bone. More commonly encountered complications of this type, however, concern the effect of subcutaneous fat layers and underlying bone for example when treating chest-wall recurrences. In the case of heating through a layer of fat it should be appreciated that excessive heating of the fat layer will occur when using capacitive techniques whilst adipose tissue is relatively transparent to microwave radiation[49] unless there is a component of the electric field perpendicular to the fat muscle interface[82]. The presence of ribs relatively close to the surface will lead to the reflection of both microwave and ultrasonic beams with the possibility of the production of local hot spots. In comparing available heating techniques such effects must be recognized at the planning stage, and taken into account in the selection of the most appropriate modality.

A physical property of the heating technique and of the applicator employed which must also be considered is the penumbra of the SAR distribution. It is clear that the SAR penumbra is not identical to the temperature penumbra due to smearing through conduction and convection. However, the sharper the SAR penumbra the sharper will be the temperature penumbra. If the target volume lies in close proximity to potentially thermally sensitive or low heat capacity normal tissues it may be necessary to select a heating modality such as ultrasound in which a steep fall off of SAR can be achieved.

A related consideration is field shaping. The flexibility to shape the heating field of a microwave applicator is very limited as the matching between the patient, applicator and generator can be impaired by the presence of reflectors. Recently developed microstrip antennae[83] do, however, permit some flexibility in the selection of the size and shape of microwave heating fields. Scanning techniques of the type employed with ultrasonic irradiation can achieve field shaping with the use of complex mechanical and control systems[80,84] control of multielement transducers has been used to the same end[30]. With capacitive heating custom designed saline bags can be used to influence the heating field[46].

Field shaping is probably most easily accomplished with interstitial techniques. Although the hyperthermia equivalent of Patterson-Parker or Quimby rules are not yet available, and in fact the development of such rules may not be possible because of living tissue dynamics, a knowledge of the heating pattern around an interstitial applicator may be used to identify with reasonable accuracy the volume likely to be raised to therapeutic temperature levels for any given configuration of applicators. The actual temperature rise achieved and its distribution will, as with any other technique, depend on heat transfer mechanisms and, in particular, on blood flow[41].

Having considered applicator performance and the likely consequences for the SAR distribution of electrical or mechanical inhomogeneities it is next necessary to assess the significance of thermal and physiological non-uniformities. For superficial sites the most common

and easily handled thermal inhomogeneity occurs at the surface. At the planning stage a decision has to be made on the required surface temperature rise and this decision will depend upon whether or not the surface forms part of the target volume. It is frequently the case that it is required to provide skin sparing and this, fortunately, is relatively straightforward. Both water cooling devices[85] which can form part of the impedance matching network and air cooling have been effectively employed. It is important to recognize, however, that very steep temperature gradients can occur at cooled surfaces and that accurate monitoring of surface temperature is difficult. It should also be recognized that whilst surface cooling obviously cannot alter the SAR distribution produced by a particular applicator it can have a significant influence on the temperature distribution even to a depth of a few cm in the tissue[86]. In particular the position of maximum temperature will be moved deeper into the tissue and be reduced in magnitude. The consequences of surface cooling will be to increase the depth at which a therapeutic temperature rise can be achieved without causing excessive temperatures more superficially and an increased requirement for absorbed power to produce the required temperatures.

Thermal and physiological inhomogeneities apart from those encountered at the surface are much more difficult to handle. In preparing the anatomical data for use in hyperthermia treatment planning it was noted that the presence and location of such inhomogeneities should be recorded. Should significant inhomogeneities exist within the treated field it must be recognized at this stage that severe temperature non-uniformities will ensue. An assessment of the likely impact of these on both the safety and likely efficacy of a hyperthermia treatment should be made early on in the treatment planning process.

The discussion to this point has reviewed the factors which will influence the choice of applicators and techniques for a particular treatment. At the current state of knowlege and computational ability a substantial amount of intuition is used to make the decisions required for hyperthermia treatment planning. Certainly the objectivity employed in assessing competing radiation

treatment plans cannot at this time be used for hyperthermia. Limited progress is however being made in this direction with some published data comparing heating systems through predicted temperature distributions in models which incorporate typical blood flows for different organs[87]. As, ideally, it is the estimated temperature distributions upon which a decision should be made such efforts will undoubtedly aid comparative thermal dosimetry.

In summary, the selection of the most appropriate heating system for a particular patient and tumour site is probably the most important decision to be made during the treatment planning process. Although the information upon which this decision can currently be based is both incomplete and almost certainly inaccurate an understanding of the physical and physiological processes which determine the distribution of temperature elevation in vivo is essential to maximize the probability of effective treatment being delivered.

4.3 Treatment Planning (Prospective thermal dosimetry)

Ideally, one wishes to carry out a prospective procedure for hyperthermia which is analagous to that routinely employed in conventional radiotherapy and with a comparable degree of accuracy. Unfortunately, in the case of hyperthermia a dynamic variable, temperature, and its distribution are ultimately required whereas in ionizing radiation therapy, the key quantity, dose is passive and merely describes the energy deposition. This difference between radiotherapy and clinical hyperthermia is chiefly responsible for placing accurate prospective temperature dosimetry out of reach at the present.

In spite of this difficulty, however, some progress in this area has been made. The first step in computing the temperature distribution in vivo is to establish the distribution of SAR. This quantity possesses the units of radiation dose rate [W/kg] and is clearly not influenced by physiological processes. Several heating modalities in routine clinical use employ coherent beams of microwaves or ultrasound and, particularly in the case of the former,

phase relationships must be taken into account. This aspect of the computation of SAR results in greater complexity than that encountered with incoherent x-ray beams. However, progress has already been made in calculating SAR distributions under realistic anatomical conditions[87,88] it is to be expected that with increases in computational speed increased accuracy will be achievable routinely. Such computations should be undertaken whenever possible as a guide to applicator selection.

As mentioned earlier the major difficulty encountered in true treatment planning for hyperthermia is translating the rate of energy absorption into temperature elevation.- Required for this-procedure is complete knowledge of the distribution of the thermal properties of the tissue being heated. The most significant of these properties is frequently convective heat loss through blood flow and the manner in which it responds to local temperature elevation.

At the moment and for the foreseeable future there is no way of establishing reliable input blood flow data upon which to base calculations of temperature. The best that can be achieved at the moment in this regard is to perform calculations based on easiest-to-heat and hardest-to-heat conditions[89] which are selected to bracket the most likely values of the actual thermal properties of the anatomical region of interest.

In summary, treatment planning for hyperthermia as understood in analogy to radiation therapy is not currently possible and indeed may never be possible. Calculations of SAR distributions, however, are being performed and with reasonable accuracy under certain conditions. whilst the information provided by such calculations is limited in its value for clinical hyperthermia, it does have several uses. Such SAR distributions permit comparative thermal dosimetry to be undertaken with more confidence and hence can lead to a more enlightened selection of the optimum heating system. Also, in the absence of gross thermal inhomogeneities the gross features of the temperature distribution will be strongly influenced by the SAR distribution. Thus, under

many conditions the locations of hot and cold spots may be predicted on the basis of SAR data to an accuracy which is sufficient to provide guidance in the clinical set up. Strong temperature gradients can be expected to accompany strong SAR gradients and the knowledge of the locations of such regions may well influence the placement of thermometers. It is recognized that slight position errors could result in significant temperature errors when gradients are strong.

4.4 Specification of in-vivo thermometry technique (Concurrent thermal dosimetry)

Thermometry during a clinical treatment is the most reliable approach at the moment to safe and efficacious therapy. It is also the most widely practised. It is clear from the previous section that accurate prospective dosimetry is not a realistic option at this time. While the optimum technique can and should be based at least on understanding, and preferably calculations of, the expected heating field, reliance cannot be placed on calculated temperature distributions carried out before the thermophysical properties of the tissues have been experimentally established.

Furthermore, although attempts are being made to develop non-invasive techniques of temperature mapping[49] these are still, at best, a long way from possessing either the accuracy or clinical utility for routine use. Thus, invasive monitoring at the time of treatment remains the only acceptable approach to clinical thermometry.

A clear limitation in determining the three dimensional temperature distribution in and around the tumour, and this, of course, is the ultimate goal, is the limited number of points at which temperature can be measured. As, for reasons of sterility, temperature probes are most commonly inserted into catheters it may be more appropriate to consider the measurements to be limited to a set of lines. In section 3.2 of this report it was pointed out that tracking techniques or the use of thermometer arrays maximizes the information obtainable from each catheter. Such techniques are to be encouraged. It is also desirable to implant as many catheters as

possible although this will be limited by the number of temperature channels which can be monitored and by patient comfort.

If the number of paths, along which temperature can be monitored is limited how are these to be chosen? A comprehensive set of animal data has strongly indicated that the most important predictor of tumour response [other factors being equal] is minimum tumour temperature[13]. On the basis of this conclusion it would appear reasonable to position at least half the available catheters along paths which intersect the periphery of the target volume.

Using the contour data produced as described in Section 4.1 together with calculated or estimated SAR distributions it is possible to identify likely cold regions of the target. Efforts should be made to ensure that catheters pass close to such points. Of equal importance are expected hot spots occurring in adjacent normal tissue. In the absence of reliable calculated SAR distributions estimates need to be made of locations of possible hot spots based on the behaviour of the applicator employed and the anatomy of the heated region. Such locations should, whenever possible, be monitored as their temperatures may pose the limit on the intratumour temperature achievable.

As a general rule it should be appreciated that temperature measurements in regions of strong temperature gradients are difficult to interpret due to the problem of locating catheters precisely at predetermined positions. Such considerations are particularly relevant when the decision is being made whether or not to monitor surface temperature. In addition it is difficult to ensure thermal contact between the thermometer and the skin without impairing surface cooling and hence influencing the parameter being measured. It is easy to question the accuracy of such surface temperature determinations. Once the efficacy of a particular surface cooling technique has been clinically established, limited thermometry channels may be more usefully employed in monitoring subcutaneous temperatures.

The placement of catheters described above has been recommended for those cases, which are the majority, where a safe and effective treatment is the sole objective. In other words, it is not the intention to attempt to reconstruct the three dimensional temperature field.

Clearly if the facilities are being developed for the derivation of the full description of the temperature field then alternative catheter arrangements may be desirable. To date some progress has been made in this respect and concerted efforts by the hyperthermia community to this end continue[90]. However, development of this important area is still limited and no recommendations can be given as to catheter placement for such purposes.

A vital aspect of in-vivo thermometry is the record and specification of thermometer location. It is a feature of the majority of published clinical reports that such information is notable by its absence. Such a short-coming undoubtedly impairs intercomparison of clinical studies and impedes the development of optimum clinical protocols. It is essential that the locations of the catheter tracks be identified as completely as possible on the patient contour data. Further it is essential that the measurement points along those tracks be reproducible and known.

Clearly an accurate technique of locating the catheter track needs to be selected and routinely employed. X-ray computed tomography is the ideal tool for this purpose as catheter location is overlaid directly on patient anatomy. If such equipment is unavailable an alternative choice is to use ultrasonic scanning which, provided the surface contour is not significantly distorted through the action of scanning, is often capable of locating the catheter position. The easiest and possibly most accessible technique in a radiotherapy department may however be the use of orthogonal X-ray films taken on a simulator. It is relatively straightforward to reconstruct the relative positions of radioopaque markers representing thermometer position[36] and, provided these can be related to patient anatomy, all the required information is obtained.

It cannot be stressed enough that recording temperatures however accurately without specifying precisely where these temperatures were measured with respect to the target volume is almost meaningless.

Concurrent thermal dosimetry has as its aim not only to confirm that an acceptable temperature distribution is achieved in and around the target but also to provide the information that permits control of the treatment. Most commonly a single applicator is employed for superficial sites and the only control available over the temperature distribution is the total power delivered - the relative temperature distribution cannot be deliberately altered. In such cases the coldest part of the target should be identified during the temperature elevation phase and this used to decide when the predetermined target temperature has been reached. Depending on the site it may be necessary to declare maximum temperatures at other locations and clearly, in such cases, several conflicting limits may be placed on the power which can be applied to the applicator. In the absence of upper temperature limits being encountered, control of the treatment is based solely on one temperature channel representing the coldest part of the target. It is important to verify regularly during the treatment that, due to, for example, temperature induced blood flow changes, the gross temperature distribution has not altered and that the control channel is indeed at the coldest part of the target. Similarly, due precautions must be taken to ensure that predetermined normal tissue temperatures are not exceeded.

With multiple applicators, eg., interstitial antennae, or with applicator scanning techniques control becomes more complex as both the magnitude of the temperature elevation and its distribution is under operator control. Here a highly interactive process will be advantageous as considerable control can be exercised over the temperature distribution produced even under conditions of changing blood flow[91].

For concurrent thermal dosimetry to be effectively implemented many decisions prior to treatment are required. Amongst these the most important are the specification of the location at which the temperature is

to be monitored and the maximum allowed and minimum desirable temperature to be attained at key locations.

4.5 Reconstruction of the treatment in time and space (Retrospective Thermal Dosimetry)

The general goal here is twofold: first, the acquisition and evaluation of a large data base of the clinical, thermal information--treatment temperatures, SAR values, and all relevant patient physical, anatomical, and medical information [ie. the standard, recommended radiological practice extended to include the hyperthermia treatment data]; second, a detailed, computer model based, evaluation of the hyperthermia treatment to attempt to extend the amount of information that can be obtained from the clinical thermometry. For this second area, since temperatures are, at blest, measured along a few tracks during clinical treatments, thus most of the locations in the tumour have not actually had their temperatures measured. This, of course, represents a very significant gap in the knowledge of what actually happened during a treatment, and is a fundamental problem for all clinical hyperthermia. For example, treatments may fail because the actual minimum temperature in the tumour is significantly less than therapeutic, even though the minimum measured tumour temperature may be therapeutically acceptable and indeed indicate that a very good treatment has occured. Thus, barring the successful technical development and clinical implementation of non-invasive thermometry techniques, one must resort to developing improved computer models of the treatments--models which use the clinically measured temperatures at the sensor locations as a basis of predicting the complete temperature field. This is, of course a very difficult problem whose successful resolution is to be considered in the future. However, given the fundamental, important nature of the expected results--knowledge of the complete temperature field--it is a problem well worth attacking. Presently, as one would expect, all of the efforts to solve this problem are in the early research stages, and no tools are available for practical, clinical application. However, the early research results look promising, with simple one dimensional layered models having been successfully used to predict experimental

results[92,93] and some early numerical and experimental results showing tha the full three dimensional problem may be solvable[90]. More progress can be expected in the future since this is a deterministic problem which can certainly be solved up to a certain level -- the limits of which are not presently known. When they are found, one may be able to answer the ubiquitious question of how many temperature sensors are needed in a treatment, and where should they be placed; questions whose answers are unknown at present.

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