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Will Thermometric Tomography Become Practical for Hyperthermia Treatment Monitoring?[1]

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Abstract

Thermal tomography refers to the acquisition of detailed thermal information throughout a slice of the subject. Experimental temperature information of this nature to be obtained experimentally using some form of scanning mechanism is usually implied by the term, noninvasive thermometry. Desirable specifications for such a system are presented, and the degree to which the proposed methods are likely to achieve these are reviewed. Four major issues that must be resolved for any system to be useful clinically are: (*a*) will the system interfere with coupling the heating source to the patient and will the physician or technologist have access as well; (*b*) will its noise rejection be sufficient to operate in the presence of strong electromagnetic or ultrasonic heating fields; (*c*) will the spatial, temporal, and thermal resolution be sufficient to record important variations during treatments; and (*d*) will the parameter sensed be a function only of temperature or will it change as a consequence of physiological variations or therapeutic effects? It is concluded that noninvasive temperature scanning is unlikely to have a significant effect on thermal therapy for many years. Conversely, invasive thermometry coupled with numerical modeling is well along the way to becoming clinically useful.

Introduction

The desirability of noninvasive thermometry for monitoring hyperthermia treatments has been advanced strongly and accepted readily for a decade. I refrain from using the stronger word, "necessity," since the last several years have shown that new methods of providing thermal therapy have been applied to human tumors as fast as new heating systems have been developed. Little hesitancy to begin treatments has been exhibited while waiting for adequate thermometry to be developed. Nevertheless, means of determining the temperature distribution throughout the heated region during therapy as well as of determining the thermal dose accumulated at every location has been shown by other papers in this supplement to be essential for predicting the response and the likelihood of a complication. Thus, noninvasive thermometric tomography is still desirable. Whether it will become practical or what type of research should be supported are questions which should be addressed.

The rationale for noninvasive thermometry is 3-fold. (*a*) Tomographic methods would give a direct measurement of the complete temperature pattern throughout the heated region. Hence, reliance on theoretical models would not be necessary. (*b*) Trauma to the patient would be reduced because invasive needles or catheters would not be necessary. (*c*) It is practically impossible to sample temperatures invasively at a sufficient number of sites to characterize the heating pattern adequately without resorting to thermal models.

The first requirement of a thermometer is that some parameter exist that is sensitive to temperature. The second requirement is that this parameter be insensitive to all other influences. In the case of probes, the thermometric medium often can be isolated from these other influences by encapsulation. In the case of noninvasive temperature sensing, such as with infrared thermography, isolation of the thermometric media (tissue surface emissions of infrared radiation) is impossible, and great care is necessary to establish the limits of error from other sources. Fortunately, skin has an emittance (27) very close to 1.0 in the wavelength band over which thermographic cameras are sensitive. This greatly simplifies their use, but not so much as to make significant errors impossible (6). For thermometric tomography, *i.e.*, determining temperature images in cross-sectional planes, the thermometric property must be stable to all other influences such as changing blood flow, percentage of water content variations, development of edema, minor position or size changes, and consequences of therapy. We suggest that each system has as goals the following specifications: (*a*) sensitivity, accuracy, and stability, 1°; (*b*) response time, 1 sec; (*c*) spatial resolution, 2 mm; and (*d*) digital storage and display. Finally, the system should be passive, *i.e.*, minimally perturbing with respect to the heating field and biologically compatible.

The next section describes briefly a number of methods of noninvasive thermometry that have been proposed. The subsequent section lists the general characteristics that are required of noninvasive thermometry systems and that proposals for such systems should address. Finally, a personal opinion is presented as a basis for discussion.

Proposed Methods of Thermal Tomography

Microwave Radiometry. This was one of the earliest methods suggested. It has been reviewed (7–9, 16) and discussed in depth in a number of papers (9, 11, 16, 18, 19, 21). It originated with the observation that noninvasive temperature sensing in tissues is similar in principle to radiometric determination of temperature profiles in the atmosphere and in free space with a Dicke radiometer. Any object above absolute zero gives off radiation as a consequence of thermal motions according to Planck's law. At the long wavelengths typical of microwave radiometers, the radiated energy is small compared to the thermal energy. Thus, Planck's expression reduces to an expression for the power received by a radiometer which is directly proportional to the absolute temperature and the frequency bandwidth to which it is sensitive. Another factor is the antenna pattern which describes the volume from which radiation is sensed. This volume is limited in depth by absorption of the radiation in intervening layers between the emitting source volume and the

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antenna. Lateral resolution is determined by the diffraction limit of the radiation which is of the order of a half-wavelength. Systems have been built for frequencies ranging from several hundred MHz (16, 19, 21) to a few GHz (11). The higher frequencies have better spatial resolution, but shallower depths of sensitivity, while lower frequencies will sense radiation emitted from a greater depth, perhaps a few cm, but have poorer spatial resolution. Typical system specifications are: temperature sensitivity, few tenths of a degree; spatial resolution, one to several cm; and integration time, of the order of a sec.

Most clinical applications of microwave radiometry have been in terms of searching for thermal anomalies that may be related to pathology. Multiple frequencies have been suggested as a means of obtaining better spatial discrimination for hyperthermia studies, but this increases the complexity of the instrumentation greatly and sensing depths are still not adequate. An interesting variation on microwave radiometry is using the same antenna for the dual purpose of heating and temperature sensing (21). While the spatial discrimination is still poor, at least one difficulty of getting both heating and sensing instrumentation around the patient is reduced. Another interesting variation on microwave radiometry is discussed later in this work in conjunction with correlation techniques.

Velocity of Sound. Measurements of the velocity of sound using transmission techniques at ultrasonic frequencies near 1 MHz also were proposed relatively early (7–9, 14, 20, 26). Because of the shorter wavelengths, the spatial resolution of ultrasonic measurements is much better. Considerable data were acquired on the characteristics of various tissues, mostly *in vitro*, but some *in vivo* as well. From these data, it was inferred that a transmission ultrasound system would have a temperature sensitivity of 0.3° and a spatial resolution of a few cm. The depth of sensing is not limited by absorption, but bones and gaseous cavities would prevent measurements in certain anatomical regions. Two difficulties arose which dampened enthusiasm for rapid development: (*a*) the velocity of sound in tissues was very sensitive to specific composition. In fact, the change in velocity with temperature was negative for fat, but positive for most other tissues; (*b*) the system was sensitive to small dimensional changes which would complicate the interpretation of the signals. A third question arose in my mind from a cursory observation of data taken *in vivo* for experiments where the tissues were raised above 42°. Does hyperthermic therapy affect the velocity of sound in a tissue? If it does, then the technique would not be a good method of thermometry. On the other hand, it might be useful as an indicator of therapeutic action. To my knowledge, this question was not investigated.

Ultrasonic Radiometry. Recently, it has been observed that the thermal motions that give rise to electromagnetic radiations within an object also will produce mechanical waves that can be sensed ultrasonically (1, 2, 9). Planck's radiation law holds here in an entirely analogous sense and reduces in a similar fashion as for microwave radiometry to an expression which is linear in temperature and the bandwidth of the receiver. However, 2 major differences exist between ultrasonic and microwave radiometry. Ultrasound has a much shorter wavelength, of the order of 1 mm, compared to one to tens of cm for microwaves. Hence, the spatial resolution is much finer for ultrasound. Also, the absorption of ultrasound in tissue, approximately 0.7 db/cm/MHz, is much lower than that of microwaves, and so depth of sensing is not a problem. The sensitivity of an ultrasonic radiometer must be very great, but appears to be within the limits of present technology. From theoretical grounds, the specifications are expected to be of the order of: temperature sensitivity, 0.1°; lateral spatial resolution, 1 to 2 cm; depth resolution, 70% of the sensing depth; and integration time, 100 sec. Ultrasonic radiometry is sensitive to temperature anomolies, but it is too soon to tell if an imaging device is possible. Furthermore, it is too soon to tell if physiological or pathological effects will alter the signal.

A variation on ultrasonic radiometry is that of thermoacoustic imaging (3, 5). In this technique, a pulse of energy is deposited in the object which produces an acoustic pulse from the slight thermal expansion at the site of deposition. It is recorded by acoustic transducers coupled on the surface. The energy pulse can be very small and can be an electromagnetic or ultrasonic heating pulse or even an ionizing radiation dose (4). Thus, a method exists for determining the specific absorption rate profile. An appealing feature is that using similar instrumentation, both a specific absorption rate and a temperature profile can be obtained. Nevertheless, this system is very early in its development. The existence of the phenomenon has been demonstrated; the measurement system is under construction.

Cross-Correlation Radiometry. If 2 receiving antennas are placed on an object and are aimed so that a portion of their patterns overlaps, then signals from the overlap region will be correlated in the 2 antennas. Signals arriving at the 2 antennas from regions outside the overlap will not be correlated. With appropriate electronics, the correlated signals can be retained and processed while all other signals are ignored. Thus, cross-correlation radiometry (9, 15, 16) permits better spatial discrimination than single aperture radiometry or even multiple aperture or multiple frequency systems. Furthermore, when the analysis is performed (9, 15), the correlated output signal is shown to be a linear function of the absolute temperature of the target region. It follows from the analysis that the effects of emissivity and attenuation of the signal by intervening layers as well as many other sources of uncertainty in other radiometric methods are eliminated. Note that the method applies to both microwaves (15, 16) and ultrasound (9, 15). Again, the instrumentation must be very sensitive, have a very high signal-to-noise ratio, and have sophisticated processing. Studies with both electromagnetic and ultrasonic radiations are underway, but I am not aware of the specifications to be expected. It appears that this method will be less sensitive to physiological or pathological processes, but this has yet to be demonstrated.

CT[2] Numbers. In calibrating CT scanners, it has been noted that the CT numbers show a temperature dependence (12, 30, 31) which is related to the density of the material and hence the density of electrons. This sensitivity is of the order of 0.4 Hounsfield units/°C. Preliminary studies (12, 30, 31) have been performed to demonstrate that a small volume plug of one temperature immersed in a phantom of another temperature can be imaged. The temperature resolution appears to be 1° or better, and the spatial resolution is a few cm, but this requires 10 min to elapse between scans. Other effects can change the electron density also; hence, the method may be sensitive to physiological changes or consequences of therapy. Finally, by the very design

[2] The abbreviations used are: CT, computed tomographic; NMR, nuclear magnetic resonance.

of a CT scanner, it is difficult to conceive of having a sophisticated heating array directed at the same patient volume as that of the temperature imager.

NMR. NMR also has been proposed as a tool to use for temperature tomography. The appeal of both this and the CT method lies in the fact that the scanners already exist. Thermal imaging thus reduces to properly using the instrument. A detailed analysis of this proposal (24) has been performed, and as for CT numbers, the results are not encouraging. The first relaxation time, T1, was suggested as the best candidate for the temperature-sensitive parameter. The temperature sensitivity of T1 is 1%/°C, which leads to a net sensitivity of better than 1°. Spatial resolution is of the order of several cm for scan times of several min. Alternatively, approximately 60 intensity measurements/min can be achieved. The suggestion was advanced that instead of mapping the entire volume, selected points could be followed instead. Also, changes in NMR signals as a consequence of therapeutic temperatures have been observed (17) (not an imaging experiment). This again would tend to reduce the interest in this method of thermometric tomography. On the other hand, NMR imaging may provide an indication of therapeutic response. Clearly, this must be investigated.

Invasive Resonators and Noninvasive Interrogation. Some of the principal difficulties in noninvasive temperature tomography are that the thermometric parameter may be small, may be sensitive to other influences, and may be difficult to localize. Another approach is to follow the rationale for interstitial hyperthermia with ferromagnetic implants. Small passive resonators can be placed surgically or transcutaneously into the region to be heated. They can be designed to have strong and specific temperature-sensitive properties and to be biocompatible. Their precise location is established by the implant procedure. They could be left in place for the course of therapy or perhaps indefinitely. Temperature measurement would be by some external, noninvasive means of interrogation. Both microwave (22) and ultrasonic[3] techniques come to mind and have been suggested. Presumably, more implanted resonators could be placed than would be possible with even multisensor probes. Nevertheless, the system would not be capable of full tomographic temperature images unless a numerical thermal model were introduced.

Multiple-Sensor Probes plus Thermal Analysis. This method has been discussed in another paper in this volume (25). I mention it here because it can be used to accomplish thermal tomography, both specific absorption rate and temperature. Its major drawback is the necessity of invasive probes. Its major advantage is the fact that it can be accomplished with existing technology. Feasibility is not in question; only time is required for producing adequate numerical models and data processing routines.

Requirements of a Thermal Tomographic System

Any proposal for a noninvasive thermometric system to be used with hyperthermia therapy must address questions related to accessibility to the patient, possible interference between the heating system and the temperature-related signal, spatial/temporal/thermal resolution compromises, and sensitivity to spurious effects such as parametric changes resulting from therapy. Array heating systems such as the BSD Annular Phased Array or the Stanford Isospherical Ultrasonic Array require intimate contact with a significant portion of the surface of the patient. It is not clear how a noninvasive temperature-sensing system could be placed to sense the same volume of tissues in which the heating system is depositing energy. Furthermore, provision must be made for the patient to be accessible to the physician and technicians running the treatments, and an ability to quickly remove the patient from the apparatus in emergency situations must be maintained. Finally, more complicated and time-consuming treatment set-ups will be welcomed by neither the patient nor treatment personnel. The existence of stray electromagnetic fields generated by the Annular Phased Array implies that the noise rejection and radiofrequency interference protection must be very high for the thermometry system. This could be difficult to achieve for the very sensitive detectors required in the systems currently proposed.

All of the systems discussed above have rather bad compromises between reading rate, temperature sensitivity, and spatial discrimination. It has been demonstrated in this volume that the minimum thermal dose achieved in a tumor is the best predictor of outcome (10) and that regional heating systems frequently leave large portions of the tumor undertreated (13, 23, 29). For proper monitoring of the treatment and for computing the thermal dose with adequate spatial resolution to be predictive, the specifications for these parameters must be better than is achieved currently. If noninvasive thermometry is to be used for real time control of the heating, then the specifications become even more stringent. However, if invasive probes are to be used for control, then some of the desirability of noninvasive scanning is lost.

Finally, questions were raised regarding many of the techniques reviewed such as whether the temperature-dependent parameter is sensitive to spurious influences. For most thermometry systems, stability with respect to ambient temperature, humidity, physical orientation, and device-specific effects are carefully noted. For the thermometric tomographic systems, an additional concern is whether the relevant tissue properties change as a consequence of therapy. If the tissue water content changes, for example from induced edema, what will be the effect on the electronic density (for CT), the proton density (for NMR), the ultrasonic velocity, or the local radiative emittance and absorption (for electromagnetic and ultrasonic radiometry)? Indeed, changes in measured parameters may lead to significant information with respect to therapeutic effects, but they will prevent computation of both temperatures and accumulated thermal dose.

An Opinion

Given the various considerations discussed here, along with the observation that hyperthermia trials will continue in the absence of even adequate thermometry, I do not believe that noninvasive temperature tomography will affect hyperthermic oncology significantly for many years. I strongly encourage research funding of basic studies to define the physical and biophysical characteristics of systems that may lead ultimately to thermal tomography, but any proposal to construct a clinical prototype should address realistically the issues raised in the above section. Insofar as progress in thermal dosimetry is concerned, an alternative exists in which there are no uncertainties

[3] J. S. Heyman, private communication.

in terms of feasibility. Only time and effort are required to develop adequate techniques and computer programs to perform retrospective thermal dosimetry based upon thermal models and temperatures measured during the treatment at several points in the heated volume. Selected papers in this volume (25, 29) as well as in a recent special issue on hyperthermia (28) demonstrate this point.

Acknowledgments

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