Development of Feedback Microwave Thermotherapy in Symptomatic Benign Prostatic Hyperplasia.

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Cell-Kill Modeling of Microwave Thermotherapy for Treatment of Benign Prostatic Hyperplasia

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ABSTRACT

***Purpose*: We investigated whether cell-kill modelling could be used as a mean for predicting the outcome of microwave thermotherapy for benign prostate hyperplasia (BPH).**

***Methods*: The two models—Henriques' damage integral and Jung's compartment model—were implemented in a computer program. Real treatment data for 22 patients with BPH who were in chronic retention were used as input, including measured intraprostatic temperatures and microwave power. To test if modelling gives results that are consistent with actual observations, comparison with transrectal ultrasound (TRUS) measurements of the prostate volume before and after treatment was made. The sensitivity of the computer model for variations in the heat cytotoxity and the temperature probe location in the adenoma was also tested.**

***Results*: The average TRUS volume reduction 3 months after treatment was 26 cc, whereas the corresponding cell kill calculation was 27 cc. The computer model appears to be rather insensitive to minor uncertainties in heat sensitivity and location of the intraprostatic reference temperature sensors.**

***Conclusion*: Cell-kill modelling appears to give results that are consistent with actual observations. The coagulated tissue volume is calculated in real time during the treatment, thereby providing an immediate prediction of the treatment outcome. By using cell-kill modelling, the endpoint of a treatment can be set individually; e.g., when a certain volume reduction has been achieved.**

INTRODUCTION

THE COSTS AND RISKS associated with transurethral resection of the prostate (TURP) and open surgery have driven the development of minimally invasive methods such as microwave thermotherapy for the treatment of benign prostatic hyperplasia (BPH). The clinical outcome of transurethral microwave thermotherapy (TUMT) has gradually improved as the technique has developed; e.g., by using intraprostatic temperature measurements to control the treatment. The indications for microwave treatment have gradually changed from solely irritative symptoms to include evident obstructive elements.[1–3]

For TURP, there is evidence of a strong correlation between the resected prostatic volume fraction and the clinical outcome.[4] We suggest that this concept applies to TUMT as well; i.e., the amount of tissue that is thermocoagulated is a primary variable for relieving the patient's outlet obstruction and symptoms. If this hypothesis is right, it should be possible to fine-tune microwave thermotherapy further by considering theoretical models of the heat cytotoxicity.[5–15] At present, microwave treatment is commonly done with a fixed duration, typically 30 or 60 minutes. A more individually tuned therapy might quantify in real time the amount of tissue that has been destroyed and continue treatment until the desired volume has been coagulated.

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ACTION OF HEAT

Damage induced by TUMT presumably follows the general pattern of burn wounds, characterized by inflammatory reactions that lead to rapidly developing necrosis and edema.[16] The injury extends, becoming wider and deeper in the days immediately after treatment because of the failure of surrounding tissues to supply borderline-viable cells with oxygen and glucose.[16,17] Microthrombi occlude vessels, and the blood flow is not adequate for cell survival, much less for repair. In the periphery, where the thermal exposure is lower, apoptosis may be the contributing cell-kill mechanism.[16,18] After the injury has reached its maximum, 2 to 5 days after treatment, a slow process of demarcation of living tissue from dead tissue begins. Healing processes are dominant, and small vessels that are still functioning regain their normal permeability and begin to remove the edema.[16,19,20] Catheterization is typically required for 2 to 14 days because of the pressure exerted on the prostatic urethral lining by the edema. After about 4 to 6 weeks, the patient will notice a considerable remission of symptoms, which is amplified over the following months.

On the cellular level, heat causes thermal inactivation of enzymes and structural proteins and rupturing of cell membranes. Replacement enzyme proteins and new membranes are synthesized over time, and recovery occurs provided the thermal exposure is not too devastating. Cell kill occurs when the damage is so severe that repair mechanisms are insufficient or when the DNA and RNA transcription enzymes that mediate repair are destroyed.[12,13,21]

Temperature and time are paramount to the creation of thermal damage: in one of the earliest studies, Moritz and Henriques[22] showed that 7 hours at 45°C caused approximately the same thermal damage on pig skin as 5 minutes at 50°C. If plotted in a diagram, with the temperature required to cause cell kill against the logarithm of the exposure time, the relation appears as a straight line with a break at about 43°C (Fig. 1); below this temperature, the inactivation rate is considerably lower for most cell lines.[12] Survival studies on mammalian cells confirm the relation to the temperature range used for microwave thermotherapy: 43° to 57°C.[12] However, different cell types and tissues may have different heat sensitivity, and this will appear as shifted but parallel curves. This observation reflects differences on the subcellular level: a change of only a few amino acids in proteins can make them more or less heat resistant.[12] A significant discovery is that in order to maintain the same biological isoeffect for a given cell line, the temperature should be increased by 1°C if the duration of treatment is shortened by a factor of two.[12]

BIOMODELS TO QUANTIFY CELL KILLING BY HEAT

In the following discussion, the term "cell kill" is used both in order to express the death of an individual cell and also in a collective sense to describe tissue death.

A model for the quantitative description of heat damage was proposed by Henriques[5] on the basis of ideas originating with Arrhenius (1889). In this model, thermal damage is thought of as a two-step process in which native biomolecules are transformed into an intermediate activated state, from which they can either relax back to their original form or proceed to a denatured, irreversibly damaged, state (Fig. 2). Henriques' "damage integral" has been used experimentally to assess the volume of heat damage.[2,5,11,14,15] The mathematical expression is:

$$\Omega = A\int e^{-Ea/(RT)}dt \qquad \text{[Eq. 1]}$$

where Ω represents the degree of injury integrated over the treatment time t, A is the Arrenius constant, E_a is the activat-

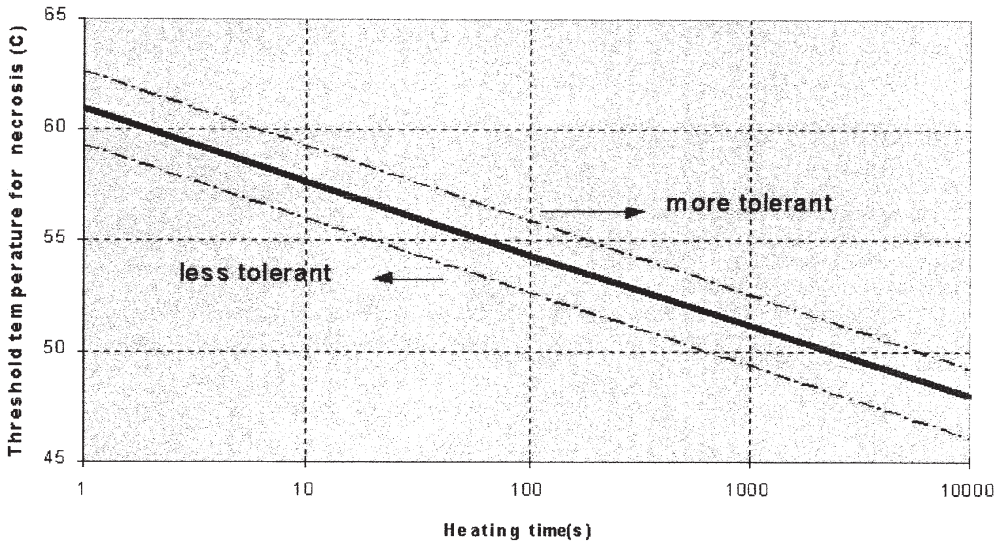

FIG. 1. Temperature required for cell killing as function of heating time. Different cell lines have different heat sensitivities, which results in shifted but parallel lines. Data from reference 5.

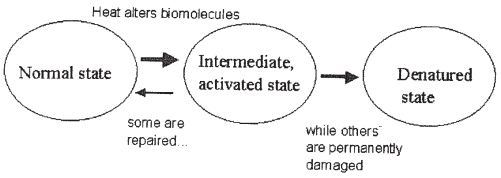

FIG. 2. Representation of Henriques' cell-kill model.

ing energy for prostate cells, R is the universal gas constant, and T is the tissue temperature.

Another model used to describe cell killing by heat was suggested by Jung,[7] who used thought compartments that are serially connected (Fig. 3). Each compartment except the top one has a tap into a common "dead cell" compartment, in which dead cells accumulate. Prior to heating, all cells are undamaged and reside in the top compartment. As heating begins, microscopic sublethal damage accumulates randomly in the cells over time. Cells with one sublethal injury occupy compartment 1, cells with two damage sites occupy compartment 2, and so on. The likelihood that a sublethally damaged cell eventually will die is dependent on temperature, time, and how many sublethal injuries it has accumulated: the more damage, the larger the probability that the cell will roll over to the "dead cell" compartment.

The model describes cell killing as a two-step process with the formation of sublethal damage that later transforms to lethal damage, but it avoids the ambiguity of Henriques' formulation by using separate temperature-dependent rate coefficients for production of sublethal damage and conversion to lethal damage, $p(T)$ and $c(T)$, respectively. Jung's model accurately predicts sensitization by step-down heating, which strengthens its claim to being biologically sound.[10]

The mathematical expression of Jung's model is:

$$\frac{dP(0)}{dt} = -p(T) \cdot P(0) \text{ for compartment 0} \qquad \text{[Eq. 2]}$$

and

$$\frac{dP(n)}{dt} = p(T) \cdot P(n-1) - p(T) \cdot P(n) - n \cdot c(T \cdot P(n) \text{ for compartments } 1,2,3, \ldots \qquad \text{[Eq. 3]}$$

where P(n) represents the probability that a cell is in compartment n, $p(T)$ represents the rate per unit time at which sublethal damage is formed at temperature T, and $c(T)$ represents the rate per unit time that sublethal damage converts into a lethal event. Initial values at time zero are P(0) = 1 and P(n) = 0 for n = 1,2. . . .

APPLICATION OF CELL-KILL MODELLING TO MICROWAVE THERMOTHERAPY

The rate of cell killing during thermotherapy depends on the intraprostatic temperature, which in turn is a function of the microwave power absorption minus the loss of heat through blood flow and heat conduction. The relation between temperature, microwave power, blood flow, and heat conduction is given by the Pennes bioheat equation.[23] In order to quantify cell killing, it is first necessary to assess the temperature distribution in the prostate. Noninvasive methods to map the temperature; e.g., magnetic resonance imaging or ultrasound,[24–26] are far from practical at present, and one must therefore measure the intraprostatic temperature directly by transducers that are inserted into the adenoma.[27,28] By extrapolation, where the measured temperatures are combined with the emitting characteristics of the microwave antenna, it is possible to assess the temperature distribution in the entire gland.[15]

There are some uncertainty factors that must be accounted for: (1) the heat sensitivity of different cell lines and individuals may differ considerably; (2) the temperature distribution in the prostate is extrapolated from a small number of interstitial measurement points in the gland; and (3) the influence of cell-kill modifiers such as thermotolerance and step-down heating may change the heat sensitivity of cells.[12] The latter exert their effects at low temperatures (<45°C) and are therefore of less importance here, because the intraprostatic temperature during treatment typically is >50°C.

Despite these uncertainties, there are several arguments in favor of cell-kill modelling as a real possibility. The most important is that killing is "digital": either a cell is alive, or it is dead. In order to achieve the intended cell killing in a specific part of the prostate, it is insignificant where the endpoint of temperature/time exposure is, as long as it is above the solid line in Figure 1. Another argument is that the microwave absorption and associated heat conduction is limited to an ellipsoidal volume approximately 40 mm in width and 30 to 50 mm in length.[29] This means that there is an upper limit to the volume that can be destroyed during treatment and hence also a limit to the possible calculation error. A third argument is that the calculation of cell killing does not need to be exceedingly accurate: it is probably adequate with a margin of error of 10 to 15 g. The benefit is still obvious: it is better for the urolo-

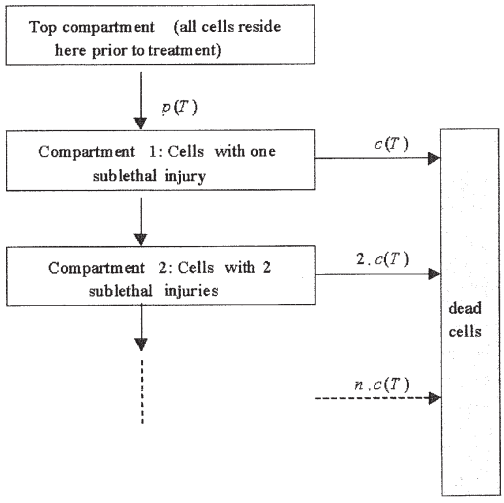

FIG. 3. Compartment model for cell killing proposed by Jung. Probability per unit time for cells to acquire sublethal damage at temperature T is p(T). Probability per unit time that cell in compartment n will die is n • c(T).

gist to know directly during treatment that, for example 45 ± 10 g of a 100-g prostate has been destroyed by heat than it is to know nothing at all about the extent of tissue destruction.

One aim of this study has been to investigate whether cell kill calculated by theoretical models is a feasible method for predicting the amount of tissue coagulation and prostate volume reduction during TUMT. The other aims were to compare different cell-kill models, to examine the implications of cell-kill modelling for the future development of thermotherapy, and to identify areas for research.

MATERIALS AND METHODS

Henriques' and Jung's models for cell killing were implemented in a finite differential computer program. The software runs in three phases. The prostatic blood flow is first calculated according to Pennes' bioheat equation[23] by taking the measured intraprostatic temperatures and the microwave power distribution as input data. The derived blood flow is then backprojected into the prostate computer model, and the temperature distribution is calculated according to Pennes' equation. Finally, the cell killing in the prostate is calculated according to Henriques' damage integral (Eq. 1) and Jung's cell-kill model (Eqs. 2 and 3). Figure 4 describes diagrammatically how the cell kill is derived according to this schedule. The thermal properties of the prostate gland were calculated from its water content, assumed to be 80%.[30]

In order to test the model, we used treatment data from 22 patients with BPH who were in chronic urine retention and received ProstaLund microwave feedback treatment between 1997 and 1999.[2] The patients volumes were measured prior to treatment and at 3 month follow-up using TRUS (B&K Medical 3535). The difference in the TRUS volumes before and after treatment was taken as a measure of the volume reduction of the prostate. To test if there was a significant difference in the results obtained by the two methods, statistical analysis comparing TRUS data with cell-kill calculations was made by calculating the variance of the difference between TRUS and cell-kill volumes. Assuming normal distribution for this difference and assuming that the mean error in a single ultrasound volume determination is 8.8 g with a standard deviation of 7.1 g,[31] we calculated a confidence interval for the standard deviation uncertainty of the cell-kill calculation. Kolmogorov-Smirnov's test to detect deviation from normal distribution was also made.

The intraprostatic temperatures were measured during treatments using an interstitial probe with three built-in sensors, which were inserted into the prostate via the treatment catheter. The sensors were positioned 15, 10, and 6 mm laterally in the left lobe relative to the catheter center and axially 10, 20, and 30 mm behind the bladder neck. Cell kill for each treatment was calculated according to the schedule shown in Figure 4 using the measured intraprostatic temperatures and microwave power (W) as input data. The radiation pattern of the microwave antenna, measured as specific absorption rate (SAR) (W/kg), was determined using the method described by Kantor and Cetas.[32]

To investigate how sensitive the cell-kill calculations are to possible errors, we have also simulated various thought fault-conditions for the 22 cases:

1. Uncertainty in the prostate cells' heat sensitivity corresponding to a difference in temperature exposure of ±1°C. This corresponds to a variation of −50% to +100% in exposure time for a given biological effect (compare Fig. 1). Each treatment was analyzed three times: with actual intraprostatic temperatures and an additional two times using the actual temperature ±1°C.
2. Error in the stated position of the temperature tip sensor of ±3 mm, which is the most likely maximal position error that can be made with the temperature probe used. Each treatment was analyzed three times: with the stated sensor locations and an additional two times using stated locations ±3 mm.

Table 1 shows the numerical values we used for parameters A and E_a in Henriques' damage integral (Eq. 1) and p(T) and *c(T)* in Jung's model (Eq. 2 and 3). Values for *p(T)* and *c(T)* have previously been reported only for CHO and C3H tumor cells, which are inherently very sensitive to heat.[7,10] Because of the lack of reference data for prostate cells, we first made simulations using data from a few reference treatments to calibrate Jung's model against Henriques' damage integral by assuming that *p(T)* and *c(T)* for human prostate cells follow the general pattern of CHO cells but are shifted toward less heat sensitivity.

RESULTS

The average prostate volume measured by TRUS prior to treatment was 79 cc (range 32–170 cc). After 3 months, it had decreased to 53 cc (range 22–138 cc). The average reduction in prostate volume 3 months after treatment thus was 26 cc. According to the cell-kill calculation, which was displayed online during treatment, the calculated destruction of tissue averaged 27 cc using Henriques' damage integral and 28 cc using Jung's formulas. There was a remarkable similarity in the results of the two models: they gave almost the same result for all cases, the average difference being 0.7 ± 1.0 cc. Figure 5 compares the individual TRUS data with the calculated cell kill according to Henriques. Error bars representing the uncertainty of the TRUS data are indicated.

From Terris and Stamey,[31] the combined standard deviation from difference volumetric measurements by TRUS was calculated to be 15.6. The 95% two-sided confidence interval for the cell-kill SD was found to be 0, 16. Because this interval covers the standard deviation by TRUS, we cannot reject the test hypothesis that the two methods have equal standard deviations. There is thus no evidence in our data that the volume of tissue destruction calculated by cell-kill modelling is less accurate than that of ultrasound measurements. Kolmogorov-Smirnov's test did not detect any significant deviation from a normal distribution ($P = 0.573$).

Simulating different heat sensitivity of the prostate did not alter the calculations significantly. The mean tissue destruction for the 22 cases shifted from 27 cc to 28 cc if the heat sensi-

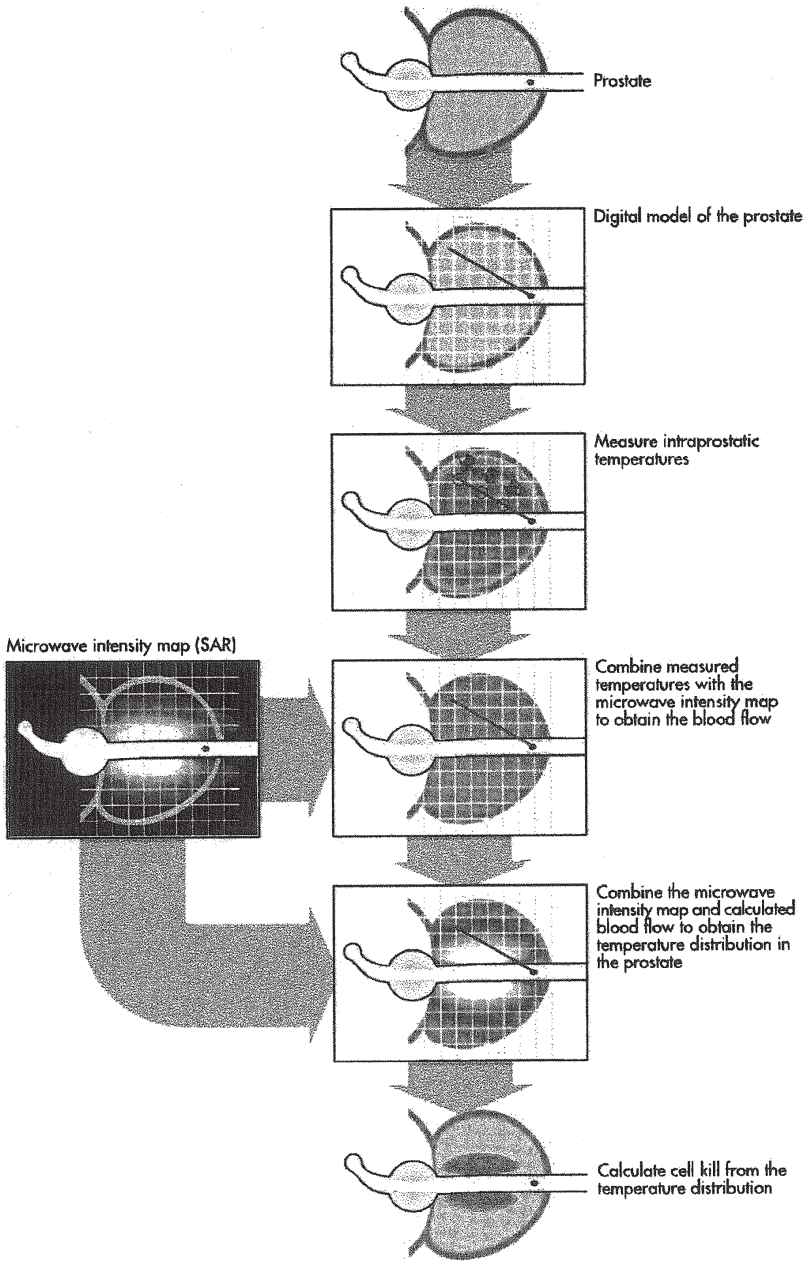

FIG. 4. Diagram of how cell kill is derived. Prostatic blood flow is first calculated: knowing microwave power distribution and temperature gives blood flow. In second step, calculation is reversed: knowing blood flow and microwave power gives temperature distribution. Last step is to apply Henriques' or Jung's formulas to obtain cell kill.

TABLE 1. NUMERICAL VALUES USED FOR PARAMETERS IN CELL-KILL MODELS

A (s^{-1})	E_a $(J\ mole^{-1})$	$p(T)$ *(dimensionless)*	$c(T)$ *(dimensionless)*
$3.1 \cdot 10^{98}$	$6.3 \cdot 10^{5}$	p(T) = exp(0.99(T-7) − 40.6)	c(T) = exp(0.34(T-7) − 15.1)

Values for A and E_a were taken from reference 5. Values for *p(T)* and *c(T)* were taken from reference 7 but shifted +7°C.

tivity was increased by 1°C and to 24 cc if the heat sensitivity was decreased by 1°C from the values specified in Table 1.

Simulating position errors of the interstitial temperature sensors likewise did not alter the calculated cell kill significantly. The mean for the 22 cases shifted from 27 cc to 33 cc if the probe tip was displaced 3 mm farther out and to 25 cc if the probe tip was displaced 3 mm closer to the catheter.

DISCUSSION

Among the advantages of microwave treatment for BPH are simplicity, safety, low cost, and the possibility of use as an outpatient procedure.[33] One weakness attributed to traditional microwave treatment is that the clinical outcome has been somewhat unpredictable: some patients respond well, while others do not. Experiments have suggested that the treatment outcome depends on a variety of factors; e.g. vessel density, epithelium:stroma ratio, prostate volume, and microwave energy.[34] We propose that all these factors are an expression of a common denominator: how much tissue has been destroyed by the heat. By using cell-kill modelling, the urologist will get an intraprocedural estimate of how much tissue has been coagulated and can terminate the treatment when a preselected extent of tissue necrosis has been achieved. A prerequisite to using cell-kill calculations is that the intraprostatic temperature be monitored during treatment and used as input in the equations.

Microwave treatments often show two distinct phases (Fig. 6). During the first phase, which typically lasts from 10 to 30 minutes, the temperature is too low to cause any significant cell killing in the prostate. A doubling of blood flow is often seen during this phase,[35] probably reflecting the vasodilation response to the elevated temperature. At a certain point, a breakthrough occurs: the blood flow begins to decrease, probably because of microthrombosis in the hottest tissue parts, which gradually grows in significance with subsequent temperature increases. After the breakthrough has occurred, cell kill devel-

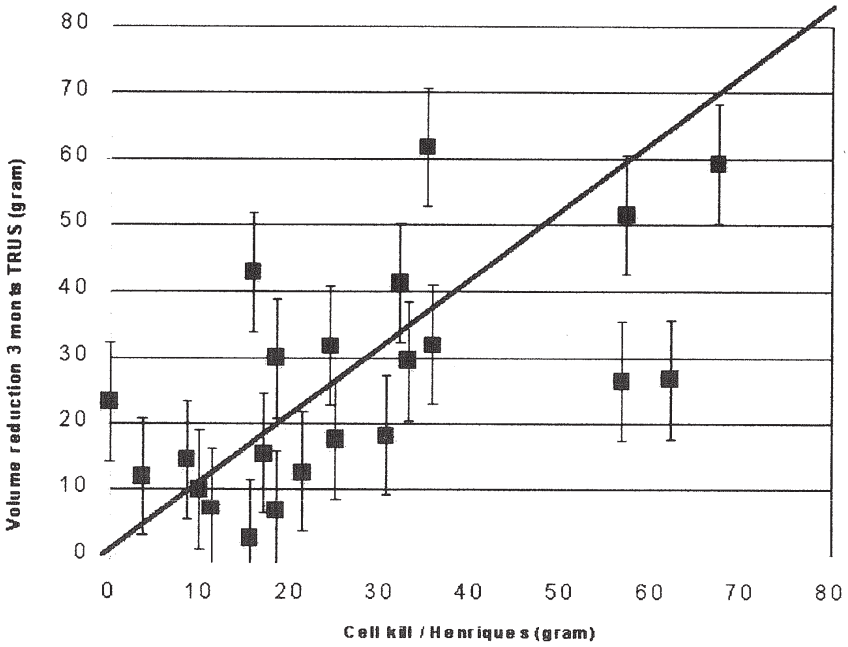

FIG. 5. Comparison of cell-kill calculation with prostate volume decrease after treatment measured with TRUS. Error bars represent uncertainty in ultrasound volume determination.

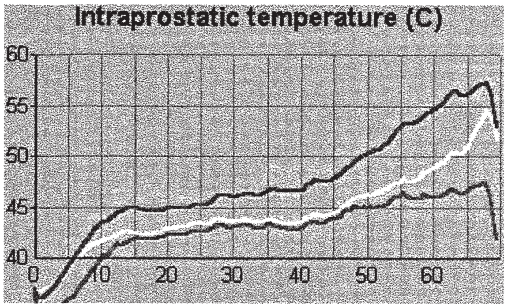

FIG. 6. Typical temperature plot during microwave treatment. Graph illustrates intraprostatic temperature at three position in left lobe: 10, 20, and 30 mm behind bladder neck at depths of 15 mm (center), 10 mm (above), and 6 mm (below) from catheter center. Rise in temperature in second half of treatment follows decline in prostatic blood flow. Cell kill occurs in this latter part of treatment.

ops fast, and substantial amounts of tissue, typically 15 to 30 g, can be coagulated relatively fast: within 10 to 15 minutes.

The computational method we used to calculate cell killing appears to be rather insensitive to minor uncertainties in the heat sensitivity of the prostate or in the position of the reference temperature sensors. At present, science lacks precise data on the heat sensitivity of stromal and epithelial tissue. In this study, because of the lack of better data, we were forced to use cell kill-rate coefficients for pig skin in the calculations.[5] There may be a systematic error attributable to this uncertainty. Nevertheless, the cell-kill calculations give results that are consistent with actual ultrasound measurements of the prostate volume reduction after treatment. In a recent study, Wagrell and colleagues,[35] who used positron emission tomography (PET) to measure changes in the prostatic blood flow during treatment and to visualize the development of the necrotic zone in the prostate, found excellent correlation between the blood flow calculated by our model and the radioisotope scans. A conclusion one thus may draw is that the heat sensitivity of prostate cells cannot be very different from that of pig skin: if it were, our method would not have matched the ultrasound and the PET study findings. In another recent study on heat-induced apoptosis in stromal cells, Brehmer and Svensson[18] found that apoptosis is the dominant killing mechanism when cells are heated for 1 hour at 47°C. Coagulation necrosis occurs at a higher temperature than apoptosis. The result from their study is thus an indirect support for our choice of cell kill-rate coefficients (compare with Fig. 1).

If the temperature v time diagram for coagulation in Figure 1 is constructed according to Figure 7, it is easier to see the causal connection to achieve successful thermotherapy. The solid line represents the threshold for creating direct cell killing by means of heat. Above the line, cells are dead, and below the

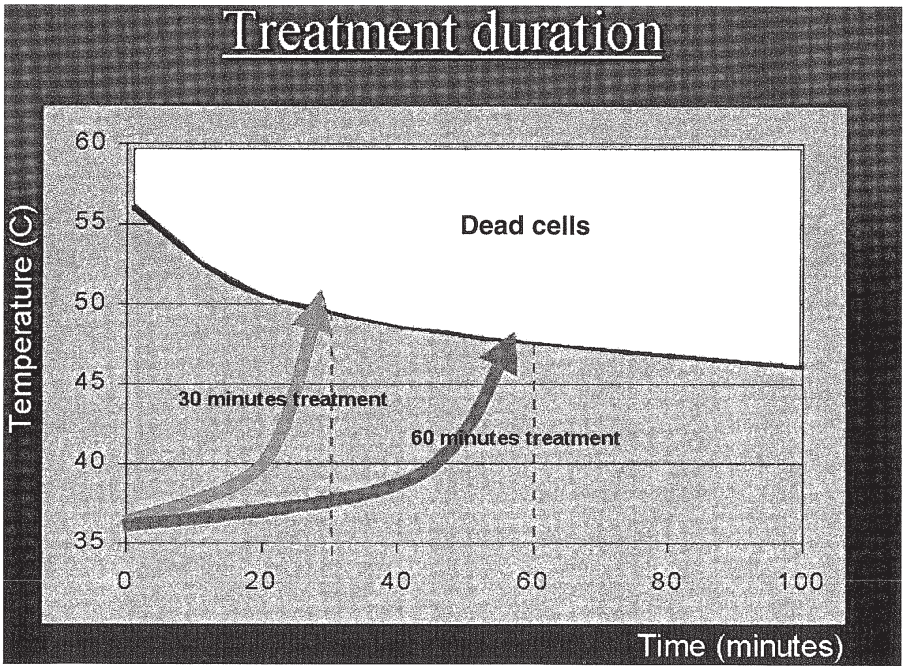

FIG. 7. In order to have intended result, heat exposure must exceed temperature represented by continuous line. Area above line expresses dead cells. In order to accomplish cell killing during 30-minute treatment, average temperature in target area must be at least 1°C higher than if treatment lasts for 60 minutes. Solid line is heat sensitivity according to reference 5. Dashed lines represent interval of uncertainty concerning heat sensitivity of ±1°C. This corresponds to uncertainty regarding exposure time of factor of two, which, according to experience, seems reasonable.

line, they are not. The arrows symbolize two commonly used treatment times: 30 and 60 minutes. In order to achieve adequate treatment, one must, according to Jung's metaphor, transfer the desired amount of cells from the top compartment, where all cells are healthy, to the "dead cell compartment," which corresponds to the dark area in Figure 7. Apparently, a more aggressive treatment and higher temperatures are required when a 30-minute rather than a 6-minute protocol is used because temperature and time are codependent. Occasionally, new treatment protocols are suggested, where the authors are driven by a well-meant desire to shorten the treatment time, but usually do not consider the basis for the entire method—heat cytotoxity.[36] By using the method outlined in this study, it is actually possible to verify treatment protocols by computer simulations before they are deployed in the clinic.

In this study, we have used temperature data from only three intraprostatic sensors located in the left lobe; it may be advisable to use more sensors to map the temperature distribution. With more sensors, it seems reasonable that the accuracy of the cell-kill modelling would increase further. Five (23%) of the patients whose data are given in Figure 5 are outliers in whom cell-kill calculation and ultrasound imaging did not match. There are several possible explanations for this variance. For example, if an intraprostatic temperature sensor is close to a large vessel, it will be cooled and show a less representative temperature. This may explain one of the three outliers. Conversely, if the sensors are placed in areas with reduced blood flow, the cell kill will likely be overestimated, which may explain the other two outliers.

CONCLUSIONS

We have demonstrated the feasibility of assessing cell killing with reasonable accuracy during TUMT. The uncertainty in the calculated data appears to be of the same magnitude as for volumetric assessment by TRUS. In the retrospective analysis of 22 patients, we found no statistically significant difference between the calculated cell kill and the volume reduction seen by TRUS 3 months after treatment. In our opinion, this constitutes an important discovery which we hope will benefit the further development of thermotherapy. Future studies in which the actual prostatic volume is determined precisely; e.g., by using ultrasound planimetry, and on the heat sensitivity of prostate cells will give additional information on the value of cell-kill modelling.

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