MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

National Library
of Canada

Bibliothèque nationale
du Canada

Canadian Theses Service

Service des thèses canadiennes

Ottawa, Canada
K1A 0N4

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

**Determination of Thermal Dose and Blood Perfusion
Rate from clinical data**

by

Elias Zakhour

**A thesis submitted to the Faculty of Graduate Studies and Research in
partial fulfilment of the requirements for the degree of Master of Science**

**Department of Physics
Carleton University
Ottawa, Ontario
November 1990**

**© copyright
1990, Elias Zakhour**

National Library
of Canada

Bibliothèque nationale
du Canada

Canadian Theses Service Service des thèses canadiennes

Ottawa, Canada
K1A 0N4

The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L'auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

L'auteur conserve la propriété du droit d'auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

ISBN 0-315-68915-3

Canada

**The undersigned recommend to the Faculty of Graduate Studies
and Research acceptance of the thesis**

**"Determination of Thermal Dose and Blood Perfusion Rate
from clinical data"**

**submitted by Elias Zakhour, B.Sc.
in partial fulfilment of the requirements for
the degree of Master of Science**

A large, stylized handwritten signature in black ink, written over a horizontal dashed line.

Thesis Supervisor

A handwritten signature in black ink, appearing to read 'P.S. Wong', written over a horizontal dashed line.

Chairman, Department of Physics

**Carleton University
November 1990**

Abstract

A method of calculating a thermal isoeffect dose by converting thermal exposure into "equivalent-minutes" at 43°C has been described by Sapareto & Dewey(1984) [36] and has been used to determine the thermal dose for the 15 patients treated by radiation followed by hyperthermia at the Ottawa Regional Cancer Center from Feb 1988 to Jan 1990.

For the purpose of this study, a reference temperature of 43°C and an Arrhenius break temperature of 43°C have been arbitrarily chosen to convert all thermal exposures to "equivalent-minutes" at these temperatures. A computer program written in Fortran 77 is included for performing calculations of "equivalent-minutes" (TD_{min}).

In order to calculate the blood perfusion rate $W(\text{ml/ml/min})$ during the cool-down period, the bioheat transfer equation has been solved for the temperatures following the power shut-down.

Acknowledgements

I would like to acknowledge my appreciation for the assistance rendered to me by my supervisor, Dr. G.Peter Raaphorst, whose helpful guidance and assistance; devotion of time; enduring patience; and confidence throughout have enabled me to complete this project.

I would like to thank Dr. R.L Clarke, Dr. P. Watson and Dr. P. Johns for their guidance during the course of my study. I would like also to thank all the members of the physics department at the OTTAWA REGIONAL CANCER CENTER for their help.

Finally, I am most thankful to my family; specially my mother and father. Their moral support and encouragement enabled me to weather the adversities of completing this degree.

Contents

1 INTRODUCTION	1
1.1 Biological rationale of hyperthermia	3
1.2 Effect of hyperthermia on normal tissue microcirculation . . .	4
1.3 Effect of hyperthermia on tumor microcirculation	4
1.4 Time-temperature relationships	5
1.5 Hyperthermia and radiation	8
1.6 Clinical treatment planning	8
1.6.1 Patient set up	9
1.6.2 Microwave Applicator	9
1.6.3 Thermometer probes	10
1.6.4 System hardware	11
1.6.5 Therapeutic temperature	11
1.6.6 Thermal injury	12
1.7 Heating problems	12

2 Thermal Dose	14
2.1 Definition	14
2.2 Theoretical Model	15
2.3 Mathematical Model	16
2.3.1 How R was calculated ?	19
2.4 Factors affecting Thermal Dose	19
2.4.1 Step-Down Heating	19
2.4.2 Fractionated Hyperthermia	21
2.4.3 Thermal Adaptation	22
2.4.4 Hyperthermia Combined with Radiation	22
2.5 Unit of Thermal Dose	23
2.6 Location of the break or transition temperature	24
2.7 Why do we need the concept of Thermal Dose ?	24
3 Blood Perfusion Rate	26
3.1 The Bioheat Transfer Equation	26
3.2 Determination of Blood Perfusion Rate (W)	28
3.2.1 The conduction term is negligible	29
3.2.2 The conduction term is not negligible, but constant	30
3.3 Implication of blood flow in Hyperthermic treatment of tumors	33
3.4 Limitations of the Bioheat Equation	35

4	Clinical Results	36
4.1	List of patients treated	36
4.2	Thermal Dose Determination	37
4.2.1	Dependence of the Thermal Dose calculations on the value of R below the break temperature and on the break temperature	40
4.2.2	Variation of the Thermal Dose with the thermal gra- dient distribution	42
4.2.3	Variation of Thermal Dose with power delivered	43
4.2.4	Variation of Thermal Dose with Tumors volume	44
4.2.5	Variation of Thermal Dose at different point location over the treatment course	46
4.3	Determination of the Blood Perfusion Rate (B.P.R)	49
4.3.1	Human tumor Blood Perfusion Rate	50
4.3.2	Tumor Blood Perfusion Rate distribution	53
4.3.3	Effect of hyperthermia on blood flow distributions . . .	54
4.3.4	Blood flow vis-à-vis Thermal Dose	55
4.4	Conduction term not negligible	56
4.5	Published clinical results	58
4.6	Clinical response	60
5	CONCLUSIONS	61
5.1	Application of the thermal dose concept	61
5.2	Application of the bioheat transfer equation	63

A Numerical results	64
B Computer program	106
C Human statistics	109

List of Figures

1.1	Family of survival curves for Chinese Hamster V79 cells at indicated temperature [42].	6
1.2	Arrhenius plots of the inverse of the slope of the heat survival curves versus the inverse absolute temperature of three cell lines heated over a temperature range from 41-46°C [42]. . . .	7
2.1	Continuous plot of temperature as a function of time for an idealized treatment shown by the dashed line and represents 120 minutes at 43°C. The three profiles (A, B, and C) are all equivalent to 120 min at 43°C by equivalent-minute calculation. 16	
2.2	Arrhenius plot of D_0 for CHO cells heated either at a single temperature (open symbols) or by step-down heating (solid squares) [5].	20
4.1	A plot of the Thermal Dose T.D (eq-min 43°C) versus R below. Data from patient no.20.	41
4.2	Variation of the Thermal Dose with channel location in the tumor. Ch 12 located at the center showed the highest Thermal Dose. Data from patient no.24	47
4.3	Plot of the Thermal Dose as a function of channel number. Data from patient no.25	48

4.4	This scattergraph shows the Perfusion Rate distribution in one patient's tumor that demonstrate a tendency toward higher flow in the tumor periphery region	54
4.5	Mapping of Blood Perfusion during the first treatment compared to that of the last three treatments in patient no.21. Channel 5 was located at the center while the rest at the periphery of the tumor	55
A.1	Channel location in the tumor of patient no.18, tumor volume is 50.0 cm ³	67
A.2	Channel location in the tumor of patient no.19, tumor volume is 18.0 cm ³	69
A.3	Channel location in the tumor of patient no.20, tumors volume are 12.5 & 3.5 cm ³	71
A.4	Channel location in the tumor of patient no.21, tumor volume is 12.0 cm ³	73
A.5	Channel location in the tumor of patient no.22, 3 nodules of volume 5.0, 1.8, and 0.2 cm ³ respectively.	76
A.6	Channel location in the tumor of patient no.23, 4 nodules of volume: 1.5, 1.0, 0.5, and 0.25 cm ³	78
A.7	Channel location in the tumor of patient no.24, tumor volume is 21.6 cm ³	80
A.8	Channel location in the tumor of patient no.25, tumor volume is 120.0 cm ³	83
A.9	Channel location in the tumor of patient no.26, tumor volume is 5.5 cm ³	85
A.10	Channel location in the tumor of patient no.27 area A, 6 nodules of volume: 2.8, 1.8, 1.2, 1.0, 1.0, 0.3 cm ³	87

A.11 Channel location in the tumor of patient no.27 area B, 3 nod- ules of volume: 1.3, 1.2, and 1.2 cm^3	89
A.12 Channel location in the tumor of patient no.28, tumor volume is 26.0 cm^3	92
A.13 Channel location in the tumor of patient no.29, tumor volume is 4.0 cm^3	94
A.14 Channel location in the tumor of patient no.30, tumor volume is 20.0 cm^3	96
A.15 Channel location in the tumor of patient no.31, tumor volume is 6.0 cm^3	99
A.16 Channel location in the tumor of patient no.32, tumor volume is 20.0 cm^3	102
A.17 Patients temperature profiles. Data from patient no.8.	103
A.18 A continuous increase in power to maintain the therapeutic temperature constant. Data from patient no.29.	104
A.19 A variation in power due to a changing in blood flow. Data from patient no.22.	105

List of Tables

4.1	List of Patients studied.	37
4.2	Thermal Dose T.D(min) and Blood Perfusion Rate W(ml/ml/min) for some of the patients studied.	39
4.3	Human tumor Blood Perfusion Rate (ml/ml/min) statistics, of the first treatment. Tables for treatments 2-4 are found in Appendix C.	52
4.4	Blood Perfusion rate with and without conduction.	57
A.1	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.18.	66
A.2	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.19.	68
A.3	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.20.	70
A.4	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.21.	72
A.5	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.22.	75
A.6	Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.23.	77

A.7 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.24.	79
A.8 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.25.	82
A.9 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.26.	84
A.10 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.27 area A.	86
A.11 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.27 area B.	88
A.12 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.28.	91
A.13 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.29.	93
A.14 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.30.	95
A.15 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.31.	98
A.16 Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.32.	101
C.1 Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statis- tics, of the second treatment.	110
C.2 Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statis- tics, of the third treatment.	111
C.3 Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statis- tics, of the fourth treatment.	112

C.4 Patients tumor average Thermal Dose (equivalent-minutes at 43°C).	113
--	-----

Chapter 1

INTRODUCTION

Hyperthermia, or elevation of temperature above levels that are not normally found in our bodies, has been used to treat a variety of illnesses for hundreds of years. One of the oldest medical texts describes the treatment of a breast tumor with hyperthermia. The description is found in the *Edwin Smith Surgical Papyrus*; an Egyptian papyrus roll which can be dated back to about 3000 B.C [12]. Records dating back to Homer's era (800 B.C) describe the heating qualities of hot steam baths in the treatment of many illnesses [87].

The Greek physician Parmenides said that given the means to induce fevers he would be able to cure all illnesses including tumors [84]. Hippocrates felt that heat was beneficial in "tumors" of the skin and stated, "Those diseases that medicines do not cure are cured by the knife. Those that the knife does not cure are cured by fire, and those that fire does not cure must be considered incurable" [87].

The more recent interest in the use of hyperthermia for cancer treatment started with the observation of the German physician W.Bush (1866) who described a patient with a histologically proven sarcoma of the face which completely disappeared after two episodes of an erysipelas infection. This infection was accompanied by an extreme febrile illness and the patient was reported alive and well without any evidence of tumor 2 years later [86].

In 1887, Bruns reported an interesting case history of a patient who was terminally ill with multiple wide-spread superficial malignant melanomas who experienced an attack of erysipelas and developed a fever of over 40°C for several days. Shortly thereafter, all tumors completely regressed and the patient was reported alive and disease free 8 years later [87].

Coley (1893) introduced febrile therapy with "mixed toxins of erysipelas and *B. prodigens*" for the treatment of malignant tumors and reported a disease-free survival of one to seven years in 3 of 17 inoperable carcinomas and 7 of 17 inoperable sarcomas. Interestingly, these original works stated that for the toxin to be effective a fever of 39°C to 40°C had to be maintained for several days [10].

Interest declined during the 1930s, due in part to the advent of anti-cancer agents; consequently, the number of studies diminished. There was then a period of renewed interest in hyperthermia, for example, in the possibility of combining heat with X-rays, but because heat application was technically difficult and therapeutic results of megavoltage radiotherapy by photons and electrons were excellent, hyperthermia disappeared again as a therapeutic agent.

In the late 1960s, a new interest in hyperthermia was initiated in several laboratories with the application of new techniques which came from studies of cell biology and radiobiology [10]. Lately, several international symposia on cancer therapy by hyperthermia, drugs and radiation have been held. These took place in Washington DC in 1975, in Essen in 1977, in Fort Collins in 1980, in Aarhus in 1984, and in Kyoto in 1988. Over several clinical experiments, it has been demonstrated that hyperthermia can improve tumor therapy if it is used as a palliative treatment modality. The curative value still has to be proven, and a number of studies have been started for this purpose [12].

This thesis is divided into four chapters:

- Chapter one gives a brief review of the biological rationale for hyperthermia with a short discussion of the equipment used during the clinical application.

- Chapter two contains the theoretical and mathematical models of the

Thermal Dose concept with the explanation of some factors affecting this dose.

-Chapter three introduces the Bioheat Transfer Equation, and discusses the calculations of the Blood Perfusion Rate from this equation.

-Chapter four shows the clinical results of the calculated Thermal Dose and Blood Perfusion Rate, of the 15 patients treated at the OTTAWA REGIONAL CANCER CENTER.

1.1 Biological rationale of hyperthermia

There are several biologic effects observed when cells or tissues are raised to temperature in the range of 41.5°C to 50°C :

a-Temperatures in that range are cytotoxic, with the rate of cell kill being dependent on temperature [88].

b-The cytotoxicity may be more prominent in cells which are at a low pH and $p\text{O}_2$; a condition often seen in tumors but not observed in normal tissues [22].

c-Hyperthermia may preferentially act in tumor tissues because it causes microcirculatory collapse at lower temperature thresholds in tumors than in normal tissues. The microcirculatory collapse deprives dependent regions of nutrients and cell death follows [24].

d-Hyperthermia has been shown to act synergistically with radiation and a variety of Chemotherapeutic drugs.

In the case of radiotherapy, hyperthermia is also complementary, because it tends to be preferentially cytotoxic to the most radioresistant cells, i.e. those in the S phase of the cell cycle and hypoxic-acidotic cells [84].

In summary, the rationale for the use of hyperthermia is strong because it is cytotoxic by itself; it tends to preferentially exploit abnormal tumor microcirculatory physiology and it is synergistic with other forms of therapy.

1.2 Effect of hyperthermia on normal tissue microcirculation

In studying the effect of hyperthermia on normal tissue vascular function, a distinction should be made between normal tissue adjacent to the tumor and that far from the tumor. Song et al. have observed that the blood flow of skin and muscle near tumors in rats was more than twice that of the skin and muscle far from the tumor and attributes this phenomenon to inflammatory process near the tumors [24]. Upon heating to 43°C for 1 hr, an increase in blood flow was seen which gradually reaches a maximum. The rise in blood flow and vascular volume depends on both the treatment temperature and the exposure time.

If higher temperatures, e.g. over 43°C are employed, the blood flow values increased faster, but after a certain period of time this was followed by a decrease to pre-heating levels or even lower. When temperatures of $45\text{--}47^{\circ}\text{C}$ are obtained, the flow values at this temperature could very well be lower than the blood flow under normothermic conditions [71].

It has also been found that hyperthermia causes a significant increase in functional vascular volume and vascular permeability in normal tissue [24].

1.3 Effect of hyperthermia on tumor microcirculation

The function of tumor microcirculation is a main determinant not only for the nourishment of malignant cells but also for the heat dissipation within the tumor. It is well established that tissue perfusion in malignant tumors is likely to vary considerably from one region to the other resulting in a nonhomogeneous overall flow distribution [86].

Hyperthermia at modest temperatures ($40\text{--}41^{\circ}\text{C}$) has been shown either to exert no effect [90] or to increase tumor blood flow [91].

Song et al. [46] noticed no significant change in blood flow in Walker 256 tumor of rat during heating at 43°C , but observed a significant decrease in tumor blood flow after termination of hyperthermia at 45°C .

Emami et al. [91] found that hyperthermia at modest temperatures ($40\text{--}41^{\circ}\text{C}$) caused either no change or a slight increase in blood flow in a rat tumor. At higher therapeutic temperatures, there was a temperature-dependent reduction in the tumor blood flow after heating, the vascular damage was irreversible after heating at $43\text{--}45^{\circ}\text{C}$, which was in agreement with observations of Song et al. [46].

It can be concluded that heating at temperatures commonly used for clinical hyperthermia results in a mild to marked and reversible increase in normal tissue blood flow. Heat at modest temperatures causes either no change or a mild and reversible increase in tumor blood flow. However, at therapeutic temperatures, hyperthermia exerts a significant detrimental effect preferentially on the microvasculature and blood flow in tumors. The temperature at which this phenomenon takes place varies depending on the species of host and the type of tumor [24].

1.4 Time-temperature relationships

It is difficult to obtain from the literature the exact temperature required for tumor cell destruction when using hyperthermia because of the wide variation of factors which influence thermal sensitivity. Environmental alterations in pH, oxygen, nutrient supply, and variation in time/dose sequence, fractionation of heat, the use of radiation and adjuvant chemotherapy, and the variation in thermal sensitivity in different cell lines all influence the critical temperature required for cell kill during hyperthermia [87].

Families of survival curves at different temperatures have been published for a number of mammalian cell lines [8, 84, 93]. A typical example is shown in Figure 1 for Chinese Hamster V79 cells [42].

Figure 1.1: Family of survival curves for Chinese Hamster V79 cells at indicated temperature [42].

An exponential rate of cell killing is found for all cell lines and the exponential portion of the survival curve is preceded by a "shoulder" region. Only a small part of this initial threshold reflects the temperature transient of the cells when culture flasks are transferred from 37°C to an elevated temperature. Some cell lines, notably Hela cells [8, 93] do not show such a "shoulder" when either the temperature transient time is small compared to the total heating time, or when an appropriate transient correction has been made. The heating rate *per se* does not appear to affect the exponential portion of the survival curve when heating rates are of the order of degrees/sec [93].

Survival curve families have been analysed in terms of the Arrhenius equation:

$$K = 1/D_0 = Ae^{-\mu/2T} \quad (1.1)$$

K is the inactivation rate constant, D_0 is the time required (at the temperature of interest) to reduce cell survival on the exponential part of the curve to $1/e$ times its initial value, the quantity A is the Arrhenius constant; μ , the activation energy; 2 is an approximation for the universal gas constant

(1.98 cal/mole); and T the absolute temperature. In this formulation, the exponential slope of the survival curve is plotted as a function of the reciprocal negative absolute temperature, where the slope of the resulting line is a measure of the activation energy (μ) of the process leading to cell death. An example is shown in figure 2.

Figure 1.2: Arrhenius plots of the inverse of the slope of the heat survival curves versus the inverse absolute temperature of three cell lines heated over a temperature range from 41-46°C [42].

The inflection point at 43°C, which has been observed for the majority of cells, is probably not a universal feature of mammalian cell killing by heat. As with the Molt 4 line, the survival data for the L_1A_2 cell line (C3H lung) shows either very little, or no inflection at 43°C [94].

The inflection point at 43°C is due to the development of thermotolerance (the development of resistance to hyperthermia), when applying chronic heating at low temperatures (40-42°C) and its latency at 43°C, that is characterized by a resistance plateau on the survival curve, see Figure 1.1. The extent of its development depends on many factors such as time and temperature of the inducing heat treatment, the environmental conditions of the

cell (pH, nutrient media, oxygen status), the cell cycle phase, cell growth state and cell type.

1.5 Hyperthermia and radiation

The rationale for the combined use of hyperthermia with radiotherapy has been that, in addition to the thermal enhancement of cellular radiosensitivity, hyperthermia is preferentially cytotoxic towards S phase cells and cells under acidic and in some cases hypoxic conditions, which cause radioresistance [24]. Hyperthermia at relatively low temperatures, e.g., 39-41°C, however, may increase the blood flow in certain types of tumors, the intratumor pO_2 may increase, which will render the tumors sensitive to subsequent irradiations [46]. Unfortunately, hyperthermia at temperatures above 41-42°C may cause vascular damage in the tumors and increase the hypoxic cell fraction. Indeed, Song et al. [46] found that the fraction of hypoxic cells in SCK tumors of mice was about 45% and it increased to about 95% at 5 hr following heating of the tumors at 43.5°C for 30 min. Although the proportion of hypoxic cells started to decrease thereafter, probably because of the death of hypoxic cells as well as reoxygenation of hypoxic cells, it was still greater than that in the unheated tumors 48-72 hr after heating. In contrast, partially hypoxic normal tissues, e.g., skin, may be better oxygenated by an increase in blood flow, which would increase the radiosensitivity of normal tissues. These facts should imply that the therapeutic gain may be greater if radiotherapy is applied prior to hyperthermia when the heat dose is sufficiently high to cause vascular damage in the tumors [8, 24, 37, 46, 84].

1.6 Clinical treatment planning

At the OTTAWA REGIONAL CANCER CENTER (ORCC), 33 patients, having superficial tumors, were treated with Irradiation and Hyperthermia between 1986 and 1990. Most of the patients received doses ranging between 3000 and 6000 cGy in two weekly fractions of 200 cGy delivered every 72 hrs, followed by heat (target temperature: 42-43°C, 60 min), which was usually

initiated within 15 to 30 min after the radiation exposure. The desired temperature was reached in most of the patients in about 10 to 15 min and timing was begun when the treatment volume exceeded 42°C .

Radiation therapy was usually delivered with electrons, energy of 9 MeV, and occasionally with Cobalt-60, in which case bolus was used to diminish the skin-sparing effect.

For the purpose of this study, only 15 patients treated from Feb 1988 to Jan 1990 were selected and their data files were analysed.

The patients were selected according to the information recorded in their files, such as; complete tumor size, channel location in the tumor, power deposited, completion of the treatment time (60 min) and course, and a complete temperature profile consisting of three components: warm-up period, period of more or less constant temperature, and a cool-down period.

1.6.1 Patient set up

In order for the patient to receive hyperthermia treatment, the patient is required to lie on a bed or couch for 60-90 min and have a small, metal cone-shaped applicator placed close to the body. A warmth is felt in the area directly beneath the metal cone. A nurse or technician will be continuously monitoring the condition. The patient however is responsible for notifying the nurse or technician if he/she becomes uncomfortable in any way or simply if the area under or near the applicator becomes too warm. The patient will be treated two times a week for one or two weeks depending on the situation.

1.6.2 Microwave Applicator

A 2450 MHz waveguide applicator with an aperture size 6x9 cm was used and positioned at about 0.5-1.0 cm above the tumor.

Microwave applicators for heating superficial tumors have received the most attention. They have several advantages compared to other applicators

(ultrasound transducers, direct contact RF electrodes, and inductive pancake coils) for superficial tumors. These include:

a-Launching an E field that is parallel to the surface. As a result there is not the problem of excessive heating of the fat layer often seen with capacitive type electrodes.

b-More uniform power deposition in the transverse plane than is normally seen with pancake inductive coils.

c-Less problems with reflections from bone-muscle or soft tissue-air interfaces than ultrasound [86].

1.6.3 Thermometer probes

Thermometer probes used in microwave-induced hyperthermia are commonly inserted into the tissue through catheters for measurement of intratumor temperatures. The insertion of a thermometer probe into a catheter increases its response time, because heat must flow through the walls of the catheter to reach the probe. Therefore, when the tumor temperature is changing, the temperature indicated by the probe lags behind the true temperature by an amount that depends on the total response time of the probe and catheter. After the tumor temperature stabilizes, the thermometer probe attains thermal equilibrium with the surrounding tissue and records its true temperature [9, 13].

The time constant of the thermometer probes used was 0.6 s. The time required for the probe inserted into the catheters to attain the true rate of change was 5 time constants, which is 3.0 s, and as the temperature was recorded each 30 s; the power was shut-off after 25 s from the previous measurement, and then a delay time of 5 s was allowed before recording the temperature, therefore we were sure that the probes recorded the true temperature.

The microthermocouple arrays used at the ORCC consist of up to 11 type K (chromel-alumel) thermocouples inside an extruded nylon sheath (internal diameter: 0.64 mm, outer diameter: 0.81 mm). The thermocouple

wire, manufactured by California Fine Wire, has a polyethylene coating and an outside diameter of 0.063 mm. The thermocouple junctions are welded together using an arc weld process. These arrays can be made with any desired spacing between the sensitive elements with an accuracy of 0.5 mm. The individual thermocouple junctions consist of discrete wire pairs rather than a common central wire to reduce axial thermal conduction.

1.6.4 System hardware

The entire system consisted of the following:

- An IBM AT computer with 640 K of memory.
- An 8087 math coprocessor.
- A colour monitor.
- A 10-megabyte hard disk.
- A hard-copy graphic plotter HP 7475.
- A Keithley 500 DAS mainframe data acquisition system which provide up to 128 channels of low-level analogue input via individual 16-channel board (AIM 7), an analogue output board, A/D and D/A conversion, a multiplexer with sampling rates of up to 3 KHz, and an absolute (cold junction) thermal reference YSI model 60 gallium cell calibration standard (29.7°C).

1.6.5 Therapeutic temperature

Hyperthermia is a form of cancer therapy where the objective is to heat the diseased tissue to some therapeutic temperature (typically 43°C). One of the difficulties with delivering this prescription is that the temperature rise in the surrounding normal tissue should be below approximately 42°C to avoid damage to that tissue [60].

Why a therapeutic temperature of 43°C ?

The rapidity with which thermotolerance develops at 41°C , and its latency at temperatures of 43°C and higher, suggest that clinical treatments of human tumors should be designed to achieve temperatures near 43°C as quickly as possible [77].

Numerous studies have shown that a temperature of 43°C for 1 hr is effective in producing both radiosensitization and cytotoxicity, and this time-temperature combination has become a clinical goal [20, 60, 84].

1.6.6 Thermal injury

The most frequently encountered thermal injury was the skin burn. The frequency of serious thermal injury has been low. The relatively low incidence of this type of injury can be attributed to the fact that active cooling of adjacent normal tissues is usually performed, and most patients are awake and can provide feedback to the therapist when tissues become excessively hot. In most studies, no correlations have been attempted between the incidence of thermal injury and measured temperature. In one report, however, the incidence of burns and blisters was positively correlated with intratumoral temperature maxima [33].

1.7 Heating problems

There are problems in the wider application of heat in cancer therapy, which are related to inadequate heating equipment to produce elevated temperatures in deep-seated tumors and to the complexities of clinical thermometry. Clinical results with hyperthermia have shown a decreased response in tumors having a depth dimension greater than 5 cm [35]. The reasons for this limitation have to do with the variation in the depth of penetration into tissue with wavelength and the size of an applicator needed to achieve a well-defined beam. First, the depth of penetration of an electromagnetic wave decreases as the frequency increases. Even at frequencies as low as 433 MHz the depth of penetration is only in the order of a few centimeters.

Therefore to obtain a depth of penetration of the order of 10 cm it is necessary to consider frequencies on the order of 10 to 40 MHz. However, at these frequencies the wavelength varies between 7.5 to 30 m in air. Since the condition necessary to achieve a well-defined beam is that the diameter of the aperture be large compared to a wavelength, it is clear that it is impossible to provide well-localized heating of deep tumors with a microwave aperture [86].

A related consideration is field shaping. The flexibility of shape of the heating field of a microwave applicator is very limited and the matching between the patient, applicator and generator can be impaired by the presence of reflectors. Recently developed microstrip antennae do, however, permit some flexibility in the selection of the size and shape of microwave heating fields [26].

Chapter 2

Thermal Dose

Thermal Dose has been identified as one of the most important factors which influences the efficacy of hyperthermia. Adequate temperature must be delivered for an appropriate period of time to the entire tumor volume in order to achieve optimal therapeutic results.

From a knowledge of the temperature during treatment as a function of time combined with a mathematical description of time-temperature relationships, an estimate of the equivalent treatment time at some reference temperature can be determined.

2.1 Definition

The concept of dose is defined in the Oxford English Dictionary (New York: Oxford University Press, 1971) as: "a definite quantity of a medicine or drug given or prescribed to be given at one time". The purpose of dose is to provide a number which relates to a specific biological response. A knowledge of the dose, therefore, provides a means of predicting the biological response to a given treatment and hence a means of communicating when one wishes to compare biological responses given in different places or at different times. It follows that the principal requirements of a dose are that it relates to

the biological response in a relevant manner, it should be a well defined and measurable physical quantity and there should be a proper means of intercomparison [31, 36, 42].

2.2 Theoretical Model

During a hyperthermia session three general temperature patterns are observed:

(a) Buildup, from the time the power is applied to the time when the prescribed temperature ($42-43^{\circ}\text{C}$), is reached.

(b) Therapeutic temperature, which represents the time at which a more or less constant temperature, is delivered at the prescribed level.

(c) A cool-down or washout period, after the power is turned off and the temperature in the tumor and the tissues decay to normal body temperature (37°C).

Integration of all of these components is essential to determine some sort of standard or comparable dose estimate for the actual treatment given. Sapareto and Dewey [36] have proposed a system, using 43°C as the reference temperature. They point out the practical application of this concept since, in cases in which the temperature is below that prescribed, the exposure time should be prolonged to correct for the reduced biological effect and, in those which the measured temperature exceeds the prescribed temperature, the treatment time should be shortened to correct for the extra biological effect.

If a treatment at some temperature is given, this may be equated with an equivalent treatment time at 43°C . Therefore, comparisons between treatments at different temperatures can be made by converting each treatment to an equivalent time at 43°C . An important extension of the use of the relationship between temperature and exposure time during hyperthermic treatments is the determination of the equivalent time at 43°C for a complex temperature history.

Ideally, the least complicated temperature history would have instantaneous temperature transitions and a period of constant temperature maintenance as shown in Figure 2.1. For ease of comparison, this is the temperature profile to which all complex profiles should be reduced [36]. By mathematically describing the temperature and time relationship, it is possible to calculate the equivalent time at a chosen reference temperature (43°C).

Figure 2.1: Continuous plot of temperature as a function of time for an idealized treatment shown by the dashed line and represents 120 minutes at 43°C . The three profiles (A, B, and C) are all equivalent to 120 min at 43°C by equivalent-minute calculation.

2.3 Mathematical Model

A number of mathematical formulations have been suggested which express temperature-time histories in terms of an equivalent time at a reference temperature, typically 43°C with units of (eq $43^{\circ}\text{C}\cdot\text{min}$). The relationship proposed by Sapareto and Dewey [36] based on the survival response of a variety

of cells to a range of temperature-time exposure has been the most thoroughly investigated to date.

The initial approach used in this study has been to calculate the accumulated exposure (t_1) from the relationship described by Dewey et al. [37]:

$$t_1 = t_2 R^{(T_2 - T_1)} \quad (2.1)$$

Where t and T are the time and temperature respectively for equivalent treatments, and R can be found either as an empirical fit of the survival data [84] or calculated as a function of the activation energy (cal/mole), μ , and absolute temperature ($^{\circ}K$), T , from an Arrhenius plot [36] as:

$$R = e^{\mu/2T(T+1)} \quad (2.2)$$

Since R is a function of temperature, for the range of interest ($37-46^{\circ}C$), the selection of R values can significantly affect the calculated dose. However, this occurs only when the actual temperature is different from the reference temperature (the R values will be discussed later on).

In reality the temperature-time relationship for any hyperthermia treatment is not a step function, but rather that it involves warming, more or less constant therapeutic temperature treatment, and a cooling phase. Each of these phases contributes to the cumulative thermal dose, and should be taken into consideration.

For sufficiently small Δt , Sapareto and Dewey [36] have expressed Equation (2.1) by a numerical integration as:

$$t_{43} = \sum_{i=0}^{final} R^{(T_{avr} - 43)} \times \Delta t \quad (2.3)$$

Where t_{43} is the equivalent time at $43^{\circ}C$, T_{avr} is the average temperature during time Δt , $\sum_{i=0}^{final} \Delta t$ = total time of treatment, $R = 2$ above $43^{\circ}C$ and $R = 4$ below $43^{\circ}C$.

The frequency with which temperature measurements are made (Δt) can affect the accuracy of the thermal dose calculation. Obviously, the more frequently the measurements (or the smaller the Δt), especially during rapid

temperature changes, the more accurate the calculated dose. On the other hand, in situations where the temperature is changing very slowly, less frequent measurements may provide sufficient accuracy.

The relationship described in Equation (2.3) provides a useful method to calculate the accumulated dose at a reference temperature under a variety of heating profiles, including those temperature histories that cannot be easily described mathematically. Obviously, it has evolved primarily from studies using single uniform doses of heat. This situation is not likely to be observed in the clinic, and complicating factors which occur during treatment fractionation must be considered. In addition the Thermal Dose calculation is strongly dependent on the choice of the R values, and I will further focus on describing these values.

Many of the studies show that above the transition temperatures of 42.5-43.0°C the value of R is approximately equal to 2 up to temperatures of 45-49°C and above and below this value the approximation of R is poor. The results of Field et al. [95] further show that *in vivo* the value of R is tissue type dependent.

The value of R at temperatures less than 42.5-43.0°C has been evaluated to lie in the range of 4-8 [31, 37, 42]. It is well known that at these lower temperatures thermotolerance develops during heating and that this could influence the slope (D_0) calculated from the survival curve and thus affect the value of R.

Therefore, R should be represented by one value from 41-49°C and $R' = R + TF$ should be the modified value for the onset of thermotolerance where TF is a thermotolerance factor [42].

Sapareto [38] suggested a single R value of 2 at all temperatures that can be used in Equation (2.3) with the addition of a dose modifying correction factor (TTDR; Thermo-Tolerance Dose Ratio) applied to reduce the dose, dependence on the degree of thermotolerance attained.

Equation (2.4) represents the form of the equation for this type of dose correction:

$$EQ43 = t_{43} = \sum_{t=0}^{final} \frac{2^{(T_{ave}-43)}}{TTDR(T,t)} \times \Delta t \quad (2.4)$$

where $TTDR(T,t)$ represents the correction factor for the thermotolerance which is a function of temperature and time.

2.3.1 How R was calculated ?

Dewey et al. (1977) [37] presented a thermodynamic analysis of cellular inactivation based on the thermodynamics of heat inactivation described by Johnson et al. (1954) and Snell et al. (1965) [42]. From this analysis the equations for Arrhenius presentation given by:

$$1/D_o = Ae^{-\mu/2T} \quad (2.5)$$

or

$$\ln(1/D_o) = \ln A - (\mu/2)(1/T) \quad (2.6)$$

were developed, where:

D_o : is the inverse of the slope on the exponential portion of the heat inactivation survival curve (Figure 1.1).

A : is effectively a constant over a narrow temperature range of 43-46°C [37, 42], and is called "The Arrhenius constant".

T : is the absolute temperature (273+°C).

μ : is the inactivation energy (cal/mole).

When data such as presented in Figure 1.1 are plotted in the Arrhenius form as shown in Figure 2.2 (open circles), the slope of the curve gives μ . Equation (2.6) and R can be calculated using Equation (2.2).

2.4 Factors affecting Thermal Dose

2.4.1 Step-Down Heating

An initial exposure of cells to temperatures above 43°C causes modification of the time-temperature relationship below 43°C. If cells are briefly ex-

posed above 43°C and then immediately treated below 43°C (this procedure is called step-down heating), the break in the Arrhenius plot seen at 43°C is eliminated (see Figure 2.2); thus an R value of 2 is valid over the whole hyperthermic temperature range [31, 36, 84].

Figure 2.2: Arrhenius plot of D_0 for CHO cells heated either at a single temperature (open symbols) or by step-down heating (solid squares) [5].

Both Sapareto et al. [36] and Hahn [84] have suggested that the development of thermotolerance causes the break in the Arrhenius plot. Exposure to temperature above 43°C inhibits or delays the development of thermotolerance, thus allowing more rapid killing when the cells are subsequently exposed to hyperthermia temperatures below 43°C . This phenomenon, of course, would affect the calculation of an accumulated dose as described below 43°C [31, 36].

Further studies are necessary to quantify the amount of hyperthermic temperature exposure above 43°C necessary to eliminate the break in the Arrhenius relationship below 43°C .

How can we define the thermotolerance?

The change in heat response induced by the initial heat treatment has been variously called "*induced thermal resistance, thermal tolerance, or thermotolerance*" [84].

Thermotolerance (the development of resistance to hyperthermia) resulting from prior exposure to heat or chemicals is an induced trait and not a selection of genetically resistant subpopulations. Chronic heating at low temperatures (40-42°C, see Figure 1.1) allows the development of thermotolerance as characterized by a resistance plateau on the survival curve. This phenomenon occurs in almost all mammalian cells but there are a few exceptions, as example; when L_1A_2 cells and Human T Leukemic cells (Molt-4) are heated at temperatures of 41-43°C they do not develop thermotolerance at lower temperatures and the data plotted in the Arrhenius form does not show a break.

Thermotolerance can also develop during incubation at 37°C after heating and the extent of its development as well as development time and decay time depends on many factors such as time and temperature of the inducing heat treatment, the environmental conditions of the cell (pH, nutrient media, oxygen status), the cell cycle phase, cell growth state and cell type.

2.4.2 Fractionated Hyperthermia

A simple calculation of equivalent time at 43°C cannot be accomplished for multiple heat doses due to the development of thermotolerance either between treatments or during protracted exposures at hyperthermic temperatures below 43°C [31, 36, 96]. As has been demonstrated clearly for a variety of cells, whether normal or malignant, previous exposure to elevated temperature produces resistance to further thermal damage, for periods of up to 6 days [97, 98]. The effect of the development of thermotolerance on the Arrhenius relationship is to cause both a shift in the break to higher temperatures and a displacement of the linear relationship toward slower rates of killing (i.e., higher D_0 values) [31, 36]. However, most importantly, the slope of the Arrhenius plot and, thus the time-temperature relationships do

not appear to change.

An additional complication of thermotolerance is the development of tolerance during the warm-up period of the heat treatment or during protracted (4 hr) exposure below 43°C . While the R value of 4 below 43°C does partially account for some of this tolerance, this technique does not completely correct for this phenomenon and requires further study.

2.4.3 Thermal Adaptation

Another factor, probably closely related to thermotolerance, is the ability of cells to modify their heat sensitivity based on the temperature to which they have become adapted [99]. It may be that the break in the Arrhenius plot at 43°C is not an absolute temperature but is, in fact, a relative temperature which becomes lower as the cells become adapted to lower normal environmental temperatures.

2.4.4 Hyperthermia Combined with Radiation

While the time-temperature relationship for combined hyperthermia and radiation interaction has not been well established and the literature contains conflicting information, evidence does suggest that this relationship is different from that for heat alone.

When heat is combined with radiation, there are two components to the increase in cell killing:

- 1- Killing from heat alone, and
- 2- Increased killing from radiation due to the interaction of heat combined with radiation [31, 36, 84].

The sequence in which the hyperthermic and radiation treatments are applied is of some importance.

Dewey et al. (1977) [37] noted that, when higher temperatures or longer treatments were used to induce thermal killing, hyperthermia preceding X-irradiation was usually slightly more effective than hyperthermia following X-irradiation; when lower temperatures were used, especially under conditions where there was no hyperthermic cell killing, hyperthermic treatment following X-irradiation was the most effective sequence. These changes associated with temperature and degree of hyperthermic killing may be related to the transition at 43°C observed in the Arrhenius plot (Figure 2.2). Thus, at lower temperatures ($40\text{--}43^{\circ}\text{C}$), the hyperthermic treatment immediately after radiation would cause increased confirmation of potentially lethal radiation damage and thus increased cell-killing [31, 36, 37, 42].

Unfortunately, in almost all of the available *in vivo* studies, no attempt has been made to adjust heating time to obtain the same "heat dose" at different temperatures for tumors.

Myers et al. [101] demonstrated that there is a rapid rise of the thermal enhancement ratio with increasing temperature or time or both. They noted that the combined data for both direct heat damage and thermal enhanced X-ray damage demonstrated that the heating time must be halved for every degree increase in temperature to achieve the same level of tissue damage.

Nevertheless, in order to truly understand the complication in calculating thermal dose for the combination of hyperthermia and radiation, further studies with homogeneous populations of cells in which heat radiosensitization is clearly separated from heat killing are necessary.

2.5 Unit of Thermal Dose

At the present time, a standard unit of thermal dose which incorporates the effects of the important biophysical variables such as heat-up time, step-down heating, thermotolerance, and thermal radiosensitization has not yet been derived.

In the case of ionizing radiation, dose is measured in terms of absorbed energy per unit of tissue (1 Gray = 100 rad; 1 rad = 100 ergs/g tissue). The

concept of absorbed energy alone is not meaningful by itself in hyperthermia cell killing. For example, a given amount of energy may increase the temperature of a cell culture to 45°C . If the system is closed and no further energy is absorbed the temperature will remain at 45°C and cell killing will proceed as a function of time without any further change in absorbed energy [42, 84]. Thus time also must be considered and dose may be a temperature time combination.

However, from *in vitro* and *in vivo* observations reviewed by Dewhirst [22] there is increasing evidence that the Thermal Dose of clinically relevant treatment can be described as equivalent-minutes of heating at 43°C .

2.6 Location of the break or transition temperature

The exact location of the break or transition temperature remains uncertain. Results obtained from Chinese hamster ovary cells suggest that it occurs at 43°C [36]. Field and Morris [95], reported in a review of *in vivo* studies in murine systems that the transition occurs at 42.5°C .

Raaphorst [40] showed that the break temperature can range from 42.5 to 44.0°C for various cell lines tested and therefore, the use of one representative temperature for the break point in clinical thermal dose calculation is inappropriate and could lead to misinterpretation of outcome.

2.7 Why do we need the concept of Thermal Dose ?

The clinical thermal treatment profile is complex in having temperature fluctuations with time, temperature gradients which change not only during treatment but also from one fraction to the next, and also variable warm-up and cool-down kinetics. It would be helpful if all of these could be represented by one parameter.

Another use of the Thermal Dose concept, is its ability to compare sequential treatments received by the same patient or to compare treatments received by several patients at different clinics.

Chapter 3

Blood Perfusion Rate

In human tissue treated by hyperthermia, blood flow is a very important parameter. It determines the microenvironment of the cells and, accordingly, the sensitivity to hyperthermia. But of even greater importance is the effect of blood perfusion on the temperature distribution in the tissue. Blood flow in the tumor and surrounding tissue is far from uniform; furthermore the body regulatory system uses variation of blood flow to control local tissue temperature.

3.1 The Bioheat Transfer Equation

The Bioheat Transfer Equation (BHTE) was originally attributed to Pennes [104]. It approximates a thermal energy balance in a specific tissue volume. The thermal energy is absorbed or distributed to surrounding biological media through the process of heat conduction and perfusion (blood flow across the sampled surface). In order to reach thermal equilibrium, energy generated or deposited into a specific volume is transferred to an adjacent element by conduction, convection, radiation, or a combination of these processes. In biological tissue the thermal transfer is complicated by heterogeneity and variable geometry of the tissue structure [58, 67].

The Bioheat Transfer Equation in biological medium is written as the balance of the heat transport mechanisms as follows [43, 51, 61, 67, 81]:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T + P + M - B \quad (3.1)$$

Where:

T = Temperature ($^{\circ}C$) at position r at time t (sec).

ρ = Density of tissue (kg/m^3).

c = Specific heat of tissue ($J/kg/^{\circ}C$).

k = Thermal conductivity of tissue ($J/m/s/^{\circ}C$).

∇^2 = Laplace operator.

P = Rate of heat production from power source.

M = Rate of heat production due to metabolic heat production.

B = Amount of heat withdrawn (heat-sink) depending on the local blood flow.

The heat removed by blood perfusion B can be expressed as follows:

$$B = W \rho_b c_b [T_v - T_a] \quad (3.2)$$

Where:

W = Perfusion rate ($ml/ml/min$).

ρ_b = Density of blood (kg/m^3).

c_b = Specific heat of blood ($J/kg/^{\circ}C$).

T_v = Venous blood temperature.

T_a = Arterial blood temperature.

If it was assumed that convective heat transfer occurs at the capillary level with blood arriving at the arteriolar connection at $37^{\circ}C$ and leaving

the venular connection at the tissue temperature, T , then the convective term B (or blood perfusion) can then be expressed as:

$$B = W\rho_b c_b(T - 37) \quad (3.3)$$

By substituting Equation (3.3) into Equation (3.1) we get:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - W\rho_b c_b(T - 37) + P + M \quad (3.4)$$

As given in the literature [30], the metabolic rate in tissue (bone, muscle, fat, skin, blood) is equal to 1.0 mW/m^3 , therefore, it can be neglected in comparison to heat deposited by the external power [43, 50, 76, 86].

We can rewrite Equation (3.4) as:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - W\rho_b c_b(T - 37) + P \quad (3.5)$$

Equation (3.5) represents the general form of the Bioheat Transfer Equation.

3.2 Determination of Blood Perfusion Rate (W)

Blood Perfusion Rate can be determined from the thermal clearance measurements by use of the Bioheat Transfer Equation when the microwave power is turned off; $P = 0$.

The cooling that occurs after the power source is turned off is governed both by conductive and convective (blood flow) heat transfer processes. In that case Equation (3.5) becomes:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - W\rho_b c_b(T - 37) \quad (3.6)$$

Equation (3.6) is used to determine the Blood Perfusion Rate (W), where several assumptions are made regarding the conduction term.

3.2.1 The conduction term is negligible

If it is assumed that conduction heat transfer is small compared to convective (blood flow) heat loss [43, 50, 51, 67, 76], and the conduction term is deleted from Equation (3.6), therefore, Equation (3.6) may be reduced to:

$$\rho c \frac{\partial T}{\partial t} = -W \rho_b c_b (T - 37) \quad (3.7)$$

By integrating Equation (3.7) over temperature and time, it becomes:

$$\ln(T - 37^\circ C) = -KWt + \ln(T_0 - 37^\circ C) \quad (3.8)$$

Where T_0 is the temperature at the beginning of thermal clearance, T is the temperature at some time, t , and $K = \rho_b c_b / \rho c$.

The Bioheat Transfer Equation in the form of Equation (3.8) predicts that the natural logarithm of the temperature difference, $(T - 37^\circ C)$, decreases linearly with time after the microwave power is turned off with a slope directly proportional to blood flow.

The blood flow corresponding to each measurement of thermal clearance is determined by performing a linear least-squares-fit of temperature and time to Equation (3.8) to obtain the slope, KW , of the best fitting straight line. Blood flow is obtained from the slope by evaluation of the constant K using values for the specific heat of muscle and blood, and the density of muscle and blood found in the literature [81].

In the determination of blood flow, the first temperature recorded after the microwave power is turned off must be excluded to allow the response time of the thermometer probe.

Sandhu [81] examined the validity of this assumption (conduction term is negligible) in the context of a spherical model. His results indicated that large error results in estimating the blood flow loss term if the distribution contains large thermal gradients. Roemer et al. [80] have also examined this problem in theory, and in conjunction with *in vivo* experiments, and have come to similar conclusions.

3.2.2 The conduction term is not negligible, but constant

Another approach to find the blood perfusion rate by solving the Bioheat Transfer Equation is to assume that the conduction term is constant and equal to a , therefore:

$$\frac{k}{\rho c} \nabla^2 T = a \quad (3.9)$$

and by substituting Equation (3.9) into Equation (3.6) we get:

$$\frac{\partial T}{\partial t} = a - WK(T - 37) \quad (3.10)$$

Now to solve this equation, a value of the constant a must be measured or calculated, by use of different methods.

1 - Method Used by Waterman (1987) [53].

Waterman described a method for determination of the thermal energy transport by conduction at the point where thermal clearance was measured. Three profiles of the tissue temperature were measured in mutually orthogonal directions about this point. The conduction term of the Bioheat Transfer Equation was evaluated from the temperature profiles by the method of finite differences (for more details see reference 53).

This method was applied on human tumor, and the blood flow was studied in five recurrent squamous cell neck tumors, 50 - 150 cm³, heated by use of external 915 MHz microwave applicator.

The rate of change of temperature that corresponds to the transport of thermal energy by conduction was found to be:

$$\frac{dT}{dt_{cond}} = \frac{k \nabla^2 T}{\rho c} = (-0.5 \pm 0.2)^\circ C/min \quad (3.11)$$

His results indicated that, the relative uncertainty in the evaluation of the conduction term of the Bioheat Equation is typically estimated to be 40%. The corresponding uncertainty in the blood flow rate will depend upon the relative magnitudes of the conduction and perfusion terms. When perfusion

is the dominant mode of thermal energy transport, the uncertainty in the blood flow rate will be less than 40%. In the example he showed in his paper, conduction was dominant and the uncertainty in the blood flow rate exceeded 100%; where in this example, the effective blood flow rate calculated from the rate of thermal decay under the assumption that conduction is negligible is 10.3 ml/100mg/min, and when the conduction term was included in the calculations, the corresponding blood flow rate is 2 ± 4 ml/100mg/min.

2 - Thermal clearance measurements from a dead pig.

A second method to determine the conduction term from Equation (3.6) is to eliminate the convective term from it, which can be done when no blood flow is present in the body. The only way to achieve that is to have thermal clearance measurements from a dead body.

Until now, no such data and measurements were found for a dead human body (a cadaver) that allows us to calculate a certain value of the conduction term and can be used in Equation (3.10) to determine the blood perfusion rate.

The only data available is the one taken from a dead pig, where the thermal clearance measurements were recorded just before and after it died. This experiment was done at the NRC in November 1986 on a pig heated by microwave applicator before and after the death. As part of this thesis the data recorded was analyzed to calculate the conduction term.

If the convective term is eliminated from Equation (3.10) (no blood flow), this equation can be reduced to:

$$\frac{dT}{dt} = a \quad (3.12)$$

Where dT / dt (of the dead pig) are determined at the beginning of the thermal decay after the power was turned off. Note that the first temperature recorded after the microwave power was turned off was excluded from the calculations to allow the response time of the thermometer probe.

The a values of the 25 channels inserted in the pig were calculated from the recorded data and a mean value was determined to be:

$$a_m = (-0.22 \pm 0.02)^\circ C/min \quad (3.13)$$

The value of the conduction term was found to be significant and affect the calculation of the blood perfusion rate depending on the rate of change of thermal gradients.

At the points of measurements, for a rate of change of thermal gradients of: $dT = (-0.20 \pm 0.02)^{\circ}C$ the value of the perfusion rate was found to be 20-40% overestimated if conduction term was assumed to be negligible, and for a thermal decay of: $dT = (-0.13 \pm 0.02)^{\circ}C$ this perfusion rate was 50-70% overestimated. To note here, that this rate of change of thermal gradient corresponds to a time interval of 0.5 s; where: $dt = 0.5$ s, and dT represents the slope of the experimental thermal decay data (such as in Figure A.17).

Therefore, a certain error results in estimating the perfusion rate if the conduction term is assumed to be negligible.

3 - Patients temperature profiles.

At the OTTAWA REGIONAL CANCER CENTER, a round applicator was used to treat a chest wall cancer that one of the patients had (patient number 8), the thermocouples inserted in the patient were 1.0 cm apart.

Channels 14 and 15 located at the center of the tumor recorded almost the same temperature ($42.5-43.5^{\circ}C$) during the first 30 min of the treatment, then, suddenly the temperature of channel 15 went gradually up to $45^{\circ}C$ until the end of the treatment even when the power was decreased by 2 watts, while the temperature of channel 14 dropped with a decrease in power and rose with an increase in power and remained in the same range $42.5-43.5^{\circ}C$ until the end of the treatment (see Figure A.17).

What can be concluded from these temperature profiles is that, for a certain reason (due to heat damage to the vasculature) the blood flow into the region where channel 15 was located, was blocked, and the cooling that occurs after the source power was turned-off was largely governed by conduction heat transfer process.

We can't confirm that there was no heat removed by blood flow but we can assume that the heat removed by blood flow was negligible compared to the heat removed by conduction process.

Therefore, the data recorded by channel 15 after the power was turned-off, was used to determine the value of the conduction term and was calculated to be:

$$\frac{dT}{dt} = k\nabla^2 T = -2.3^\circ C/min \quad (3.14)$$

Psoriasis patients treated with hyperthermia showed the same reaction during the treatment where the temperature of several channels was seen to rise when the power was dropped 10 watts (due to a drop in vascular blood pressure), and the conduction term calculated, by assuming convective term negligible, was found to be:

$$\frac{dT}{dt} = k\nabla^2 T = (-1.7 \pm 0.3)^\circ C/min \quad (3.15)$$

If comparing the values of (3.14) and (3.15) to the values of (3.11) and (3.13) we can see that there is a certain difference which can be explained by the fact that probably there still is some perfusion during the cooling process of the patients and, therefore, these values (3.14) and (3.15) can't be used to replace the conduction term in the calculation of the blood perfusion rate.

What can be concluded from (3.11) and (3.13) that the value of the conduction term is somewhere between $-0.7^\circ C/min$ and $-0.2^\circ C/min$ and this value must be considered when calculating the blood flow rate and, therefore, the assumption made by some researchers in neglecting the conduction term is not acceptable especially when blood flow is low, and more research should be done to find out an acceptable value, for normal and cancerous human tissues probably by using cadavers. These are not available to us.

3.3 Implication of blood flow in Hyperthermic treatment of tumors

The blood flow in tumors varies considerably among different tumor types, ages, and sizes [46]. Even in the same tumor, the distribution of blood perfusion and vasculature is quite heterogeneous. The tumor blood flow generally decreases as the tumors grow larger, owing partially to progressive deterioration of vascular beds due to the rapid growth of tumor cell population

relative to vascular beds [24]. Blood flow in tumors may or may not be greater than that in the surrounding normal tissues at normothermic conditions. Compared to the normal tissue blood flow, however, the capacity of tumor blood flow to increase upon heating appears to be rather limited. Consequently, the heat dissipation by blood flow in tumors is slower than that in normal tissues, and thus the temperature of tumor rises higher than that in normal tissue during heating. Preferential heating of tumors, however, may not be achieved all the time because the relative blood perfusion in some tumors remains greater than that in the surrounding normal tissues despite the profound increase in normal tissue blood flow during heating [24, 46].

The vasculature in tumor can be significantly damaged at temperatures which may alter but do not damage the vasculature of normal tissue. Upon heating, the intratumor environment becomes acidic, hypoxic, and nutritionally deprived due probably to vascular damage. Such a suboptimal environment in the heated tumors potentiates the response of tumor cells to hyperthermia, inhibits the repair of thermal damage, and also interferes with the development of thermal tolerance. The acidic environment also appears to potentiate the response of tumor cells to certain drugs at elevated temperatures. The change in oxygenation of tumors and normal tissues caused by the changes in blood flow may have significant implications in the effectiveness of different sequences of hyperthermia and radiotherapy in the combined use of these two modalities. Changes in the distribution of drugs in tumors and normal tissues due to changes in blood flow will also determine the optimal use of hyperthermia in conjunction with Chemotherapy [24, 43, 46].

The rise in temperature of tissues during heating is largely dependent on the influx of heat from the external heat source and also on the efflux of heat through dissipation by the circulating blood [64, 68]. Therefore, preferential heating and damage of tumor can be expected only if heat is preferentially delivered to the tumor or if heat dissipation by blood flow is slower in the tumors than in the surrounding normal tissues [46, 69].

It is now an established fact that an acidic and nutritionally deprived environment greatly increases the thermosensitivity of tissue, inhibits the recovery of tissue from thermal damage, and perhaps inhibits the development of thermotolerance [88, 90, 95].

The outcome of a combined use of heat with radiation would also be influenced by the heat-induced changes in blood flow and resultant changes in oxygen supply in tumors and normal tissues. The increases in blood flow in some types of tumors at relatively low temperatures may lead to an increase in oxygenation of tumors and, thus, an increase in the response of the tumors to subsequent radiation. Usually, the oxygen supply in normal tissue is adequate and heat induced increases in blood flow would have no further effect. The data accumulated during the last several years suggests that an application of heat before X-irradiation exerts a more radiosensitizing effect on normal tissues than on the tumors. It would be reasonable to attribute the above phenomenon to deterioration of blood circulation in tumors and a concomitant increase in the blood flow in normal tissues, and thus pO_2 in tumors would decline resulting in radiation resistance while pO_2 in normal tissues would remain the same. [46, 59, 64, 66, 71, 84].

3.4 Limitations of the Bioheat Equation

The Bioheat Transfer Equation is limited in modeling the effect of blood circulation on the local tissue temperature due to fundamental assumptions in solving the model with appropriate boundary and initial conditions. The convective heat transfer term ignores the direction of capillary perfusion and the influences of large vessels surrounding the local tissue. The original Pennes's Bioheat Transfer Equation solves for the temperature distribution in homogeneous medium with isotropic thermal properties. The inherent limitations assumes blood flow is nondirectional at the capillary level, physically suggesting that capillaries are randomly oriented with respect to their arteriolar and venular connections [82, 86, 89].

Regardless of the limitations of the Bioheat Transfer Equation, the equation formulated by Pennes (1948) has been useful for predicting many trends in hyperthermia applications.

Chapter 4

Clinical Results

The calculated Thermal Dose (T.D) and Blood Perfusion Rate (W) of the 15 patients treated (patient no.18 to no.32 as selected from the clinic), from Feb 1988 to Jan 1990, with radiotherapy followed by hyperthermia at the Ottawa Regional Cancer Center are presented in this chapter.

4.1 List of patients treated

In order to study the results of the calculated Thermal Dose and Blood Perfusion Rate, complete information regarding the patient's tumor volume, tumor site, number of probes inserted for temperature measurements, and number of treatments received, are necessary and listed in Table 4.1.

This information was taken from the patients files, where the tumor dimensions and it's depth below the skin, measured by X-ray imaging, are recorded and enabled us to estimate the tumor volume.

Patient No.	No. of treatments	Tumor(s) volume cm^3	Tumor site	No. of probes
18	2	50.0	left side of neck	5
19	4	18.0	Upper anterior chest wall	2
20	4	12.5 & 3.5	Left neck	2
21	4	12.0	Lower neck anterior	2
22	4	5.0, 1.8 & 0.2	Lower abdomen	3
23	4	1.5, 1.0, 0.5 & 0.25	Chest wall	2
24	4	21.6	Right tibia	3
25	2	120.0	Sternum	3
26	4	5.5	Right Sub-clavicle	3
27A	4	2.8, 1.8, 1.2, 1.0, 1.0 & 0.3	Chest wall	2
27B	4	1.3, 1.2 & 1.2	Right chest wall	2
28	2	26.0	Left neck	2
29	2	4.0	Chest wall	3
30	4	20.0	Left chest wall	3
31	2	6.0	Anterior abdominal wall	3
32	4	20.0	Anterior chest wall	4

Table 4.1: List of Patients studied.

4.2 Thermal Dose Determination

A method of calculating a thermal isoeffect dose by converting thermal exposure into equivalent-minutes at 43°C has been described in Chapter 2 and was used in this thesis to determine the Thermal Dose.

For the purpose of this study, a reference temperature and a break temperature of 43°C have been arbitrarily chosen, and a value of 4 for R below the break temperature has been used, while the value for R above the break temperature is 2.

A computer program written in Fortran 77 is listed in Appendix B for performing calculations of equivalent-minutes at 43°C (T.D).

It has been shown that the break temperature for cells in culture can be determined by direct cell killing experiments, but this can not be done for human tissues, therefore, the choice of the break temperature at 43°C has been chosen as a best estimate from all available data [27, 30, 32, 35, 42]. However, there is evidence that this temperature may vary from 42.5 to 44.0°C [42] and that it may be a relative temperature related to the normal physiological temperature of the tissue rather than an absolute value.

The objective of our study was to draw some trends during the treatment course, and try to find some correlations between:

- a- Thermal Dose and Power deposited.
- b- Thermal Dose and Thermal gradients.
- c- Thermal Dose and Perfusion Rate.
- d- Large tumors versus Small tumors.

Therefore, Table 4.2 illustrates the variation of the Thermal Dose (T.D) calculated, from treatment to treatment, as a function of power delivered, tumor location, and Blood Perfusion Rate (W), for some of the patients, and complete details on each patient are shown in Appendix A. Also Table C.4 illustrates the average Thermal Dose of all the treatments sessions.

Patient no.25					
Treatment No.	1	2	3	4	Channel location
T.D	14	22	-	-	Ch 9
W	1.8	3.2	-	-	Center
T.D	23	42	-	-	Ch 19
W	2.5	4.2	-	-	Periphery
Power/Time	(10-22)W/ 73 min	(10-30)W/ 73 min	-	-	
Patient no.28					
T.D	0.0	0.0	-	-	Ch 3
W	9.9	4.4	-	-	Deep center
T.D	56.0	128.0	-	-	Ch 23
W	7.5	3.9	-	-	Superf center
Power/Time	(10-48)W/ 74 min	(10-36)W/ 74 min	-	-	
Patient no.26					
T.D	300	888	4234	3083	Ch 12
W	6.5	5.7	5.7	3.8	Center
T.D	2.0	0.0	4.0	6.0	Ch 23
W	9.4	6.5	5.8	3.9	Periphery
Power/Time	(10-30)W/ 71 min	(10-32)W/ 65 min	(10-42)W/ 69 min	(10-30)W/ 64 min	
Patient no.27B					
T.D	8.0	3.0	19	38	Ch 14
W	4.2	4.8	4.2	3.5	Center
T.D	2.0	2.0	5.0	16.0	Ch 13
W	3.8	4.2	4.0	3.4	Periphery
Power/Time	(10-20)W/ 60 min	(10-25)W/ 70 min	(10-23)W/ 70 min	(10-32)W/ 68 min	

Table 4.2: Thermal Dose T.D(min) and Blood Perfusion Rate W(ml/ml/min) for some of the patients studied.

4.2.1 Dependence of the Thermal Dose calculations on the value of R below the break temperature and on the break temperature

The value of R for temperatures below 42.5-43.0°C has been evaluated to lie in the range of 4-8 [31, 37, 42]. Therefore, in the computer program written to perform the calculation of the Thermal Dose, the value of R below the break temperature had been varied from 4-8, and the results showed that the Thermal Dose decreased when increasing the value of R below from 4-8, as shown in Figure 4.1, and this Thermal Dose is reduced 50-70% for an equivalent-minutes at 43°C less than 10 min, 34-48% for an equivalent-minutes at 43°C between 11-20 min, 18-28% for an equivalent-minutes at 43°C between 21-30 min, 6-14% for an equivalent-minutes at 43°C between 31-50 min, and less than 4% for an equivalent-minutes at 43°C greater than 50 min.

In fact, when applying the Thermal Dose concept, an exact value of R below the break temperature can not be calculated. As seen in Chapter 2 the value of R is calculated when knowing the activation energy of the cells that is determined from the Arrhenius plot determined by direct cell killing experiments. This can't be done for human tissues.

Figure 4.1: A plot of the Thermal Dose T.D (eq-min 43°C) versus R below. Data from patient no.20.

The same attention must be paid on choosing the break temperature as found to vary between 42.5 and 44.0°C , and when an appropriate value is determined for specific cells, a mathematical formulation must be developed to convert the equivalent-minutes calculated at the break temperature (if different from 43°C) to an equivalent-minutes at a reference temperature chosen to be 43°C . For the simplicity of our calculations, the break temperature was chosen to be the same as the reference temperature (43°C) in a way to avoid any conversion, because the conversion form presented in Sapareto's model [36] was found to be unable to handle this conversion, and this work is still in progress.

4.2.2 Variation of the Thermal Dose with the thermal gradient distribution

In all the patients studied, the thermal gradient distribution was found to vary during the treatment course with different tumor volume. The size of the thermal gradients, as reported in the literature [33], can be related to the characteristics of the heating technique, efficiency of coupling tissue, and tissue blood flow. Both tumor volume and site have also been observed to influence thermal gradients, probably because they have different blood flow and may also influence power deposition patterns.

Biologically, the intratumoral thermal gradients would be expected to influence tissue responses to heating since hyperthermic damage is known to be related to both temperature and time.

The thermal gradient distribution within the heated tumors was found to vary from $1.0^{\circ}\text{C}/\text{cm}$ to $4.0^{\circ}\text{C}/\text{cm}$, where Gibbs et al. [32] reported an intratumor thermal gradient variations of 1 to $3^{\circ}\text{C}/\text{cm}$, and as this temperature gradient gets larger with more power deposition during the treatment, the deviation of the Thermal Dose calculated gets larger from one point location in the tumor to another.

This trend has been seen in patient no.19 (Table A.2, and Figure A.2), during the first treatment. Channel 3 was recording the lowest treatment temperature that is 39.7°C and channel 16 the highest temperature that is 43.7°C , leading to a thermal gradient of $2.0^{\circ}\text{C}/\text{cm}$, the power delivered during the treatment was (10-52)Watts for 48 min and the Thermal Dose was determined to have an equivalent-minutes at 43°C of 0.5 min for channel 3, and 65 min for channel 16. During the second treatment, the power used was increased (10-55)Watts for 49 min and with a thermal gradient of $2.5^{\circ}\text{C}/\text{cm}$, the Thermal Dose determined for channel 3 remained the same, while the one calculated for channel 16 has increased by 75%, with the notation that the blood flow of channel 16 increased only from 3.4 to 3.6 ml/ml/min.

In some other patients even when keeping the same amount of power delivered over the treatment course, the thermal gradient was found to decrease from one treatment to another, resulting in a reduction in the Thermal Dose

variation, and thus changing of thermal gradient was due to an increase in blood flow.

Therefore, what can be concluded from the patients studied, that within the heated tumor volume, there was a trend toward a great deviation of the Thermal Dose from one point in the tumor to another when there was a large thermal gradient distribution within the heated tumor.

Any reduction in the blood flow from treatment to treatment can produce a decrease in the thermal gradients which may diminish the deviation of the Thermal Dose distribution in the heated tumor.

4.2.3 Variation of Thermal Dose with power delivered

As seen in Chapter 2, a temperature profile for treatment consists of three components: warm-up period where the power was rapidly increased to reach the therapeutic temperature ($42-43^{\circ}\text{C}$), a period of more or less constant temperature where the power has to be adjusted to maintain a constant temperature, and a cool-down period after the power was shut-off. Looking at the first period, as the blood flow increases during the treatment, more power is required to elevate rapidly the temperature to reach the therapeutic temperature of $42-43^{\circ}\text{C}$ which must be kept constant during the treatment time (60 min), the heat removed by conduction and blood flow must be replaced by another amount of energy transferred from the power generator. In fact it was seen in 60% of the patients, when the blood flow increased, a continuous increase in power was required, to replace that amount of heat removed in order to keep the therapeutic temperature constant (see Figure A.18).

If vascular damage occurred during the treatment, the blood flow is expected to be reduced, and therefore, less power is required to keep the therapeutic temperature constant. This was noticed in 15% of the patients treated especially in small tumors having a volume less than 6 cm^3 . In 15% of the patients, where no change in blood flow was observed, a constant power was

able to keep the therapeutic temperature more or less constant, since the heat transfer remains the same (see Figure A.19).

In the rest, 10%, there was a trend toward a continuous adjustment of the power delivered either due to a changing in blood flow, or, to a thermal damage to normal tissues surrounding the tumor where blisters were seen after the treatments (case of patients no.20, 27A, and 32, see Appendix A). In some case a rapid rise in temperature in a particular point in the tumor was noticed, which required a decrease in power to respond to the patient's condition, who was complaining from an intolerable hot area due to the elevation of the temperature above 46°C (case of patients no.19, 22, 23, 32, Appendix A) (see Figures A.17, and A.19).

Therefore, variation in the power deposited during the treatment followed by an alteration of the blood flow affected the treatment temperature profile, and, as the Thermal Dose is a summation of the temperature over all the treatment time, it was affected by this fluctuation of temperature. A low temperature profile reached during the treatment (less than 41.5°C) resulted in a low Thermal Dose less than 12 equivalent-minutes at 43°C , a treatment temperature profile between $42-43^{\circ}\text{C}$ resulted in a Thermal Dose equivalent to 20-60 equivalent-minutes at 43°C and for temperatures profiles higher than 43°C a high Thermal Dose greater than 60 equivalent-minutes at 43°C was reached.

4.2.4 Variation of Thermal Dose with Tumors volume

The variation of Thermal Dose with tumors volume was determined as shown below:

- For tumors of volume $50-120\text{ cm}^3$, the Thermal Dose was found to vary from 2-42 equivalent-minutes at 43°C .
- For tumors having a volume between 12 and 26 cm^3 , a Thermal Dose ranging from 1 to 241 equivalent-minutes at 43°C was found.
- For small tumors, volume less than 6 cm^3 , a Thermal Dose was calculated to vary from 1 to 406 equivalent-minutes at 43°C , with the exception

of one tumor which had a high Thermal dose of 4234 equivalent-minutes at 43°C .

This high Thermal Dose was found in only one tumor having a volume of 5.5 cm^3 (patient no.26, Table 4.2), this tumor probably had a necrotic center. The blood flow was calculated to be 6.5 ml/ml/min in the first treatment, 5.7 ml/ml/min in the second and third treatments, and 3.8 ml/ml/min in the fourth treatment. The thermal gradients were found to vary from $8\text{--}10^{\circ}\text{C/cm}$ during the treatment course, and this large gradient can lead to the conclusion that these blood flow rates are not representative and this may be a case of high conduction term, where in the case of large thermal gradients, a large error results in estimating the conduction term negligible as indicated by Sandhu [81]. However, in 60% of the small tumors studied, the Thermal Dose was found to be higher than in larger tumors.

In both, large and small tumors, the distribution of the temperature within the tumor volume was found to be nonhomogeneous, as also reported by Carlos et.al [25], and Strohbehn [34], therefore, the Thermal Dose calculated was found to be nonuniform.

Looking at a tumor of volume 5.5 cm^3 (patient no.26, Table 4.2) where the highest Thermal Dose and highest treatment temperature ($48\text{--}50^{\circ}\text{C}$) were found, it was concluded that this may be due to vascular damage. When we compare it to a tumor of about the same volume 5 cm^3 (patient no.22, Table A.5), we can see a great difference in the Thermal Dose calculated, that is likely due to a necrotic tumor in patient no.26.

Also the tumor site has been also realized to have a certain effect on elevating the temperature in the tumors, where the nodule of patient no.26 located at the right-clavicle was more thermo-sensitive (tumor becomes less resistant and responds well to the heat, and therefore, more cell killing occurs) than the nodule of patient no.22 located at the lower abdomen (see Table 4.1 for tumors location).

4.2.5 Variation of Thermal Dose at different point location over the treatment course

The temperature of different points located at different places in the tumor was recorded under a channel number that refers to a specific point location in the tumor. 14 to 27 channels were used per tumor per treatment to record the temperature during the treatment. The Thermal Dose of the channels (or points) located at the edges or at the tumor was excluded from our study, because we were only concerned about the Thermal Dose of the heated volume. The channels placed along the skin near the tumor were used only to record the skin temperature in order to avoid any thermal burns to the skin that leave the patient in pain.

In 70% of all the tumors treated, the channel located at the center of the tumor recorded the highest temperature, as also reported by Sijens et al. [28], Carlos et al. [25], and by Dewhirst et al. [33], leading to a higher Thermal Dose (see Figure 4.2, and Figure A.7, where channel 12 located at the center had the highest Thermal Dose).

Figure 4.2: Variation of the Thermal Dose with channel location in the tumor. Ch 12 located at the center showed the highest Thermal Dose. Data from patient no.24

In 20% of all the tumors the channel(s) located at the periphery recorded higher temperature than the one located at the center, and therefore, higher Thermal Dose. Figure 4.3 and Figure A.8 illustrates a case where channel 20 located at the periphery had the highest Thermal Dose calculated.

This particular patient (no.25) had a combined treatment of hyperthermia and chemotherapy, which may have allowed the drug to concentrate at the peripheral area more than at the center of the tumor, causing vascular damage to the peripheral area. The blood flow was noticed to be lower at the peripheral than at the center region of the tumor, and therefore, the temperature in this region was observed to rise higher, leading to a higher Thermal Dose (see comments in Table A.8). In some other patients (as in patient no.30; comments in Table A.14) an adjustment of the applicator was required during the first treatment which might have lowered the applica-

tor toward the peripheral area, where channels 2 and 3 are located. As a consequence, more power was deposited in this region than in the center of the tumor, causing vascular damage and reduction in the blood flow at the peripheral area, that would have allowed the temperature to increase more, and thus, the Thermal Dose was calculated to be higher at the periphery than at the center of the tumor.

Figure 4.3: Plot of the Thermal Dose as a function of channel number. Data from patient no.25

Several factors were seen to affect the temperature distribution in the tumor during the treatment course:

- Variation of power delivered during the treatment period.
- Changes in blood flow due to vascular damage that occurs during or after the treatment.
- Patient condition affected by a painful high temperature that required the use of a cooling agent such as a fan during some periods in the treatment.

All these factors played a major role in the variation of the therapeutic

temperature profile, of a specific channel location, from treatment to treatment, and therefore, the Thermal Dose calculated was found to change during the treatments sessions.

In 65% of the patients studied, there was a trend toward an increase of the Thermal Dose during the treatment course, in 25% a fluctuation in the Thermal Dose was found, and in 10% a trend toward a decrease in the Thermal Dose was noticed.

Large tumors ($50-120 \text{ cm}^3$) have showed a reduction of the Blood Perfusion Rate that resulted in an increase in the Thermal Dose during the treatments sessions, while 75% of smaller tumors (less than 26 cm^3) have shown a trend toward a decrease in the Thermal Dose from first to second treatment and then it fluctuated in the rest of the treatments probably dependent on the degree of vascular damage induced in these tumors.

4.3 Determination of the Blood Perfusion Rate (B.P.R)

The Blood Perfusion Rate was determined from the thermal clearance measurements by use of the Bioheat Transfer Equation, as described in Chapter 3, when the power was turned-off, and is given by:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - W \rho_b c_b (T - 37) \quad (4.1)$$

The cooling that occurs after the power source was turned-off was governed both by conductive and convective (blood flow) heat transfer processes.

In this study, we approximated blood flow by assuming that conductive heat loss is negligible in comparison to blood flow heat loss, and the conduction term was deleted from Equation (4.1), which became:

$$\rho c \frac{\partial T}{\partial t} = -W \rho_b c_b (T - 37) \quad (4.2)$$

However, thermal conduction is expected to be present to some degree and probably is seldom negligible. Whenever thermal conduction is significant

the blood flow determined by measurement of thermal clearance will be systematically in error as will be shown in the next section.

Integrating Equation (4.2) over temperature and time it becomes:

$$\ln(T - 37^{\circ}\text{C}) = -KWt + \ln(T_0 - 37^{\circ}\text{C}) \quad (4.3)$$

Where:

T_0 = Temperature at the beginning of thermal clearance

T = Temperature at some time t and position r

$K = \rho_b c_b / \rho c = 1.104$

ρ_b = Density of blood (1060 kg/m³)

c_b = Specific heat of blood (3900 J/kg/°C)

ρ = Density of tissue (muscle) (1070 kg/m³)

c = Specific heat of tissue (muscle) (3500 J/kg/°C)

Data taken from reference [81].

The first temperature recorded after the power was turned-off was excluded to allow the response time of thermometer probe as described in Chapter 1. The Blood Perfusion Rate corresponding to each measurement of thermal clearance was determined by performing a linear least-squares-fit of temperature and time to Equation (4.3) to obtain the slope, KW , of the best fitting straight line. The Blood Perfusion Rate was obtained from the slope by substituting the value of $K = 1.104$.

4.3.1 Human tumor Blood Perfusion Rate

The tumor Blood Perfusion Rate calculations were determined from 54 hyperthermia treatments of 15 different human patients.

Table 4.3 shows general statistical information from 14 patients in which such calculations were made from the data of the first treatment. Statistical informations regarding the rest of the treatments data are included in Appendix C.

The data points refer to the number of separate intratumor calculations obtained in a particular patient's tumor.

Average (mean) Perfusion Rates varied from (1.9 ± 0.5) to (16.4 ± 8.8) ml/ml/min, a factor of about 8. Median Perfusion Rates reflected the averages quite closely and had a similar range of variation. The median Perfusion Rate of the patients with the two smallest tumors with those of the two largest were compared. Patients no.23 and 27 areaB had tumors of volume less than 1.5 cm^3 corresponding with tumor Blood Perfusion Rate values of 5.8 and 4.4 ml/ml/min, while patients no.13 and 25 had tumors of 50 and 120 cm^3 corresponding with Perfusion Rates values of 2.1 and 2.2 ml/ml/min, respectively. While the differences in Perfusion Rate between tumors at the extremes of size exhibited a trend, there was not a significant correlation between Perfusion Rate and tumor size when all of the 14 patients tumors were analysed. In addition to the intertumor variability there was significant intratumoral variability in Perfusion Rate. For example, in patient no.21, first treatment, up to a 5-fold difference in Perfusion Rate was noticed from one sampled area to another, and in patient no.32, fourth treatment, up to a 17-fold difference in Perfusion Rate was observed. These differences could result from the thermal vascular damage to a certain location in the tumor more than others.

Patient no.	No. of data points	Average B.P.R	Median B.P.R	S.D	Range
18	22	2.2	2.1	0.85	1.0-4.4
19	7	4.1	4.3	1.47	2.4-6.3
21	7	16.4	18.5	8.8	2.9-26.4
22	8	1.9	1.8	0.5	1.2-2.6
23	3	6.1	5.8	1.85	4.6-7.8
24	10	7.2	5.9	4.5	2.6-16.9
25	14	2.3	2.2	0.45	1.6-3.3
26	8	7.6	7.0	2.12	5.2-11.2
27A	9	4.2	4.1	0.77	3.1-5.4
27B	6	4.5	4.4	1.1	3.0-5.7
28	5	5.7	5.3	3.26	2.6-9.9
29	3	6.3	4.3	2.25	4.3-8.2
30	10	10.5	10.4	3.1	6.4-16.2
31	11	2.3	2.1	0.6	1.4-3.4
32	9	6.2	6.5	1.37	3.6-7.7

Table 4.3: Human tumor Blood Perfusion Rate (ml/ml/min) statistics, of the first treatment. Tables for treatments 2-4 are found in Appendix C.

4.3.2 Tumor Blood Perfusion Rate distribution

The distribution of Blood Perfusion Rate in tumors was evaluated to determine if blood flow varied randomly throughout tumors or if there were systematic variations between the center and periphery of tumors.

A scattergraph plot (Figure 4.4) shows an example of the flow distribution in one patient's tumor. These data are taken from patient no.26 (see Table A.9), who had a 5.5 cm^3 tumor located at the clavicle. Each point on the scattergraph is a Perfusion Rate value determined from the temperature decay during the cooling process as shown in section 4.3. The y-axis represents magnitude of Blood Perfusion Rate and the x-axis the channel number referred to a point location in the tumor. Channel 12 located at the center of the tumor showed the lowest Blood Perfusion Rate compared to those located at the periphery.

It was observed in 80% of the patients, that there was a tendency toward higher Perfusion Rates in the periphery region.

Figure 4.4: This scattergraph shows the Perfusion Rate distribution in one patient's tumor that demonstrate a tendency toward higher flow in the tumor periphery region

4.3.3 Effect of hyperthermia on blood flow distributions

The blood flow distribution in tumor in the first initial hyperthermia treatment (trt 1) compared with three later treatments (trt 2, 3, 4) in one patient's hyperthermia treatment course is displayed in Figure 4.5. This particular patient (no.21) had a 12.0 cm^3 tumor located at the lower neck. The decision to evaluate changes in flow distribution retrospectively between the first and the second treatments was due to an observation that a change in tumor heating characteristics occurred at this time, both with respect to the maximum temperature attained and the temperature gradient from center to periphery. In addition, the power / treatment time ratio rose suddenly between treatments 1 and 2. Subsequently, the values in treatments 2-4 were fairly constant. It was hypothesized that the change might be due to an alteration in blood flow (Oleson et al. [64]). Indeed, in this case an abrupt reduction in the blood flow calculated in the peripheral region of tumor after the first treatment

suggests a physiological effect from hyperthermia, while that in the low flow center remained relatively constant (see Table A.4).

Figure 4.5: Mapping of Blood Perfusion during the first treatment compared to that of the last three treatments in patient no.21. Channel 5 was located at the center while the rest at the periphery of the tumor

4.3.4 Blood flow vis-à-vis Thermal Dose

When analyzing all the 15 patient's tumors, there were no specific correlations that can be drawn between Blood Perfusion Rate and Thermal Dose.

In large tumors ($50-120 \text{ cm}^3$, patients 18 and 26) there was a trend toward a reduction in the Blood Perfusion Rate (see Table 4.3, and Tables C.1) when the Thermal Dose was noticed to increase due to an increase in the power deposition during the treatment course (see Tables A.1, and A.8), and this trend was more noticeable, at the center of tumors than at the peripheral regions, where only 75% of the points located there exhibited that trend and the rest showed an alteration (an increase or a reduction) in blood flow.

Smaller tumors (less than 26.0 cm^3) exhibited a trend toward a decrease in Blood Perfusion Rate that was followed by an increase in Thermal Dose, either due to an increase of the power deposited during the treatment course, or to vascular damage in the tumors from previous treatments. The points located at the periphery had higher Blood Perfusion Rate than the ones located at the center, that can be related to the failure of hyperthermia to damage the peripheral area of the tumors, where more heat removal can be expected.

4.4 Conduction term not negligible

Heat transport by thermal conduction was assumed to be negligible in the derivation of Equation (4.3); however, thermal conduction is expected to be present to some degree. When thermal conduction is not negligible, the blood flow determined from the slope of the thermal clearance curve will contain a systematic error. The magnitude of this error can't be accurately determined because the rate of temperature change due to thermal conduction can't be distinguished from that due to perfusion.

Sandhu (1986) [81] examined the validity of this assumption in the context of a spherical model. His results indicated that the conduction term can be neglected under the conditions of negligible thermal gradients at the point of measurements, and a large error results (more than 40%) in estimating the blood flow loss term if the distribution contains large thermal gradients. Roemer et al.(1985) [80] have also examined this problem in theory, and in conjunction with *in vivo* experiments, and have come to similar conclusions.

Therefore, it is well proven that this conduction term cannot be neglected and should be considered when calculating the blood flow from the Bioheat Transfer Equation. The question is: What value can be used, and will it be applied on all the patients ?

Up to now, not much work has been done to express a range of values or a single value that can be used. Waterman (1987) [53] expanded the Laplacian of the temperature and then used the method of finite differences to express each term of the Laplacian, he tested his model on a static phantom and then

on human tumors where he inserted three orthogonal thermocouple probes at the point of measurements, and he came out with a value of $(-0.5 \pm 0.2) ^\circ\text{C}/\text{min}$ for the conduction term, from which he concluded that the blood flow rate in his case would have been overestimated by at least a factor of 2 if conduction was assumed to be negligible.

The value of $a = -0.5^\circ\text{C}/\text{min}$ was substituted into Equation (4.1), and the Blood Perfusion Rate, of our patients, was calculated to be 10-80% overestimated if the conduction term was deleted from Equation (4.1).

From the pig data (see section 3.2.2), the conduction term in muscle was calculated to be: $-0.22^\circ\text{C}/\text{min}$. This value was also substituted into Equation (4.1), and the Blood Perfusion Rate was determined to be 5-30% overestimated if the conduction term was deleted from Equation (4.1).

Table 4.4 compares the flow rates calculated with and without conduction. Data are taken from patient no.19.

Patient no.19				
Channel 5	Treatment 1	Treatment 2	Treatment 3	Treatment 4
conduct=0	4.4	3.3	5.4	4.7
conduct= $-0.22^\circ\text{C}/\text{min}$	3.6	2.3	4.5	4.1
conduct= $-0.5^\circ\text{C}/\text{min}$	1.3	1.0	3.6	2.9
Channel 16				
conduct=0	3.4	3.6	4.8	3.2
conduct= $-0.22^\circ\text{C}/\text{min}$	2.4	3.1	4.2	2.7
conduct= $-0.5^\circ\text{C}/\text{min}$	1.03	2.8	3.5	0.6

Table 4.4: Blood Perfusion rate with and without conduction.

What can be concluded from this table:

1 - The conduction term must not be deleted from the Bioheat Transfer Equation when calculating the Blood Perfusion Rate, because the results may be overestimated.

2 - The error in estimating the blood flow gets smaller if the conduction term was taken to be $-0.2\text{ }^{\circ}\text{C}/\text{min}$ instead of $-0.5\text{ }^{\circ}\text{C}/\text{min}$.

3 - The conduction term is not a constant, but a variable.

Therefore, more research must be done to solve the problem of the conduction term.

4.5 Published clinical results

The statistics presented in Table 4.3 and in Appendix C showed a considerable variation in the magnitude of tumor blood flow.

From Table 4.3, average flow values of less than 10 ml/ml/min were seen in 13/15 patients (87%) while values between 10 and 20 ml/ml/min were observed in 2/15 (13%).

From Appendix C:

-Second treatment: average flow values of less than 10 ml/ml/min were seen in all the patients (100%).

-Third treatment: average flow values of less than 10 ml/ml/min were seen in 9/11 patients (82%) while values between 10 and 20 ml/ml/min were observed in 2/11 (18%).

-Fourth treatment: average flow values of less than 10 ml/ml/min were seen in 8/11 patients (73%) while values between 10 and 20 ml/ml/min were observed in 3/11 (27%).

Mantyla (1979) [102], in studies using ^{133}Xe clearance to determine blood flow in 35 unheated human cancer nodules, reported that 49% had flows of less than 20 ml/ml/min; 34% were between 20 and 40 ml/ml/min and 17% were in the range 40-60 ml/ml/min. Waterman et al.(1987) [43] observed the same results. Thus, the results of our study are qualitatively similar in that high blood flow values were relatively uncommon.

In a recent review, Acker et al.(1990) [64] concluded that 71% of the patients have flows less than 10 ml/ml/min, about 18% between 10 and 20 ml/ml/min. These findings are in general agreement with our results.

Song (1984) [66] in a review on the effect of local hyperthermia on blood flow and microenvironment, reported that the blood flow in 0.2 and 0.5 g tumors in mammary adenocarcinoma of Fisher rats was 11.2 and 9.5 ml/ml/min in the smaller and larger tumors, respectively, after heating for 1 hour. These data are difficult to compare to findings of our study because of the difference in tumors size, but there seemed to be a certain correlation between the tumor size and blood flow, that is, as the tumor gets larger the blood flow decreases, correlation that might relate to the low blood flow in our patients.

The intratumoral heterogeneity found in our study has been reported by several investigators. For example, Dewhirst (1989) [103] reported data showing heterogeneous intratumor blood flow with consequent foci of relative hypoxia and acidosis. In addition, the observation that the blood flow in the peripheral area of the tumor was greater than that in the tumor center is in agreement with previous studies investigating this possibility (Song et al.(1984) [46], Acker et al.(1990) [64]). Song [46] reported that the relatively good blood perfusion and efficient heat dissipation may be responsible for the failure of hyperthermia to damage the peripheral area of tumors.

The abrupt changes in blood flow that occurred between hyperthermia treatments, suggesting a physiological effect from hyperthermia, have been also reported by Acker et al. [64]. Such changes have been observed by Song [46] in murine models as well.

In summary; we find that human tumor blood flow magnitudes and changes are markedly heterogeneous.

4.6 Clinical response

After the treatment sessions were terminated, no long term follow up of the patients was made in order to evaluate the tumor response to the combined radiotherapy and hyperthermia treatments.

From the patients files, either from the notes registered or from the photos taken after the treatment course, we were able to determine that 6/15 patients who returned to the department after 4-6 weeks from the last treatment showed a complete tumor response, and the tumor was completely gone, 4/15 of the patients whom photos were taken straight after terminating the last treatment, showed 50-70% tumor regression, and there were no informations regarding the rest.

We also observed that tumors less than 26 cm^3 exhibited better response than larger ones, where a trend toward a higher temperatures being delivered to the small tumors was noticed.

Due to the variations in blood flow and pH, evidence suggests that tumors are likely to show large differences in their sensitivity to heat. The same observations were reported by Perez and Sapareto (1984) [25, 31], and their clinical results showed that an average of 56% of the tumors treated exhibited a complete regression, and 30% showed partial regression.

During the treatment, it is important to avoid any thermal burns, which we observed in 4 patients (about 27%, Perez et al. [25] observed burns in 6% of the patients), probably related to technical factors (such as design of applicators, coupling techniques, etc..) and can be avoidable. Most of these burns were superficial and healed with conservative management. Careful skin care is mandatory, and the avoidance of infections, particularly by anaerobic bacteria, are critical to achieve good healing [31].

Chapter 5

CONCLUSIONS

5.1 Application of the thermal dose concept

From the statistical results presented in Appendix C; Table C.4, one can see the variation of the thermal dose during the treatment course, and from patient to patient.

It can be concluded that the application of the thermal dose concept for clinical treatment is difficult regarding the variation of several factors affecting the treatment, such as:

- a-Non-uniform power deposition during the treatment course.
- b-Variation of the blood flow from treatment to treatment as a result of vascular damage.
- c-Non-steady applicator position during the treatment course, where some adjustments were required due to excessive heating resulting in pain felt by the patient in the area directly beneath the applicator.
- d-Tumor volume, where small tumors of volume less than 6 cm³ have showed to have higher thermal dose than larger tumors which was due to inadequacy of the heating equipment to produce elevated temperatures in deep-seated large tumors.

Looking back at Equation (2.3) that was used to calculate the thermal dose, we can see the dependence of the equivalent-minutes at 43°C of two major terms:

1-The value of R below the break temperature which was found to vary from 4-8 [36, 42] that can affect the calculated thermal dose having an equivalent-minutes at 43°C of less than 50 min (see section 4.2.1).

2-The location of the break temperature that was found to be between 42 and 44°C, and was taken in this study to be at 43°C.

Therefore, more research must be done to determine the exact location of the break temperature of the tumor treated, with the evaluation of the appropriate value of R below that break temperature. Once these terms are found a conversion form must be established to handle the conversion of the equivalent-minutes calculated at the break temperature to an equivalent-minutes at the reference temperature (43°C).

In terms of heating problems, the 2450 MHz waveguide applicator used at the Ottawa Regional Cancer Center can heat tumors having a depth not greater than 1.5 cm. This must be replaced by a 915 MHz waveguide applicator able to heat tumors having a depth dimension up to 5 cm, and therefore, an elevated temperature can be produced in deep-seated tumors (large tumors) where an increase in tumor regression can be expected that might lead to a complete tumor response to the hyperthermic treatment.

A related consideration is field shaping. The flexibility of shape of the heating field of a microwave applicator is very limited and the matching between the patient, applicator and generator can be impaired by the presence of reflectors. Recently developed microstrip antennae do, however, permit some flexibility in the selection of the size and shape of microwave heating fields [26], that can reduce or avoid any thermal injury to the normal tissue surrounding the tumor. These can keep the patient in a steady condition during the treatment resulting a more uniform power deposition in the heated volume.

5.2 Application of the bioheat transfer equation

The use of the bioheat transfer equation to calculate the blood perfusion rate was found to be governed by the energy lost by conduction and convection after the power was shut-off.

The assumption made by several investigators to neglect the conduction term was found to be inconsistent, where the blood flow calculated was found to be overestimated by a significant factor when this term is deleted from the bioheat transfer equation.

The only available values of the conduction term were:

1- $(-0.5 \pm 0.2)^{\circ}\text{C}/\text{min}$ measured by Waterman (1987).

2- $(-0.22 \pm 0.02)^{\circ}\text{C}/\text{min}$ from a dead pig (1986).

For more details see section 3.2.2.

Therefore more research must be done to determine this conduction term either by having thermal measurements from a dead human body (a cadaver), or by the use of Waterman's method that consists in measuring the temperature in mutually orthogonal directions about a point that can be selected to be at the center of the tumor. Here the blood flow was found to be lower than the periphery region and therefore the relative importance of the conduction term in this region is of greater significance than in the peripheral region of the tumor.

Appendix A

Numerical results

Patient no.18			
Treatment no.	1	2	Channel no.
T.D	0.7	1.7	0
W	1.0	3.4	
T.D	6.7	5.5	1
W	1.5	2.1	
T.D	4.4	12.1	2
W	1.5	3.1	
T.D	2.6	9.2	3
W	1.3	2.0	
T.D	1.2	2.2	4
W	1.5	1.3	
T.D	0.6	0.8	5
W	1.4	1.7	
T.D	0.6	0.5	6
W	1.3	1.5	
T.D	0.3	0.0	7
W	1.3	1.0	
T.D	0.0	0.0	8
W	2.3	1.5	
T.D	16.3	41.9	10
W	2.2	2.5	
T.D	6.0	6.5	11
W	2.3	1.3	
T.D	1.2	0.0	12
W	3.5	0.8	
T.D	5.7	0.0	15
W	4.4	-	
T.D	3.1	0.0	16
W	4.1	-	
T.D	1.1	0.0	17
W	2.1	-	

Patient no.18, continued			
T.D	0.5	1.1	19
W	1.8	1.1	
T.D	0.8	3.0	20
W	1.8	1.0	
T.D	0.9	3.7	21
W	2.4	2.0	
T.D	1.4	9.2	22
W	2.1	0.6	
T.D	2.4	5.8	23
W	2.2	0.8	
T.D	4.4	8.8	24
W	2.2	0.8	
T.D	11.1	24.0	25
W	2.4	2.8	
T.D	5.0	2.6	26
W	2.3	1.2	
T.D	1.3	0.7	27
W	2.1	0.3	
power/ time	(18-49)W/ 56 min	(22-50)W/ 53 min	

Table A.1: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.18.

COMMENTS:

No discomfort was noticed during the two treatments.

Figure A.1: Channel location in the tumor of patient no.18, tumor volume is 50.0 cm³.

Patient no.19					
Treatment no.	1	2	3	4	Channel no.
T.D	0.0	0.0	0.0	0.0	1
W	-	2.3	12.7	4.4	
T.D	0.2	0.4	0.2	0.2	2
W	20.3	2.6	6.8	3.7	
T.D	0.5	0.5	0.3	0.9	3
W	6.3	2.6	4.4	3.6	
T.D	1.4	1.1	1.2	9.9	4
W	3.3	2.8	4.6	4.2	
T.D	10.5	8.9	12.0	13.5	5
W	4.4	3.3	5.4	4.7	
T.D	6.1	15.0	12.2	0.7	6
W	4.8	3.6	5.5	4.7	
T.D	1.1	2.2	0.5	0.3	7
W	2.7	3.2	6.0	5.9	
T.D	0.3	0.6	0.2	0.1	15
W	2.4	2.6	4.8	3.2	
T.D	65.0	113.4	92.3	0.3	16
W	3.4	3.6	4.8	3.2	
T.D	15.7	14.7	5.0	89.2	17
W	4.3	2.8	3.3	4.4	
T.D	0.8	0.8	0.2	0.6	18
W	2.4	2.7	3.4	3.0	
power/ time	(10-52)W/ 48 min	(10-55)W/ 49 min	(18-55)W/ 43 min	(15-40)W/ 24 min	

Table A.2: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.19.

COMMENTS:

A lot of pain during treatments.

Probe (1): Spacing 0.5 cm

Probe (2): Spacing 1.0 cm

Probe (3): Surface, spacing 1.5 cm

2 probes spaced 1.2 cm

Figure A.2: Channel location in the tumor of patient no.19, tumor volume is 18.0 cm³.

Patient no.20				
Treatment no.	2	3	4	Channel no.
T.D	3.5	0.4	0.5	1
W	7.8	12.8	29.0	
T.D	6.2	0.6	0.5	2
W	7.8	9.5	23.4	
T.D	11.3	3.1	1.6	3
W	7.4	15.0	13.2	
T.D	74.0	10.9	5.2	4
W	7.4	9.4	12.5	
T.D	83.4	103.3	36.6	5
W	5.9	9.6	16.1	
T.D	103.6	168.2	148.0	6
W	5.6	8.4	12.8	
T.D	76.1	74.0	46.8	7
W	6.3	11.1	17.5	
T.D	65.8	24.6	6.2	8
W	7.2	8.9	20.3	
T.D	5.6	1.4	0.1	15
W	5.9	7.7	25.0	
T.D	49.5	45.3	2.0	16
W	4.3	8.4	24.8	
T.D	1.8	1.2	26.2	17
W	4.3	11.4	11.4	
T.D	9.0	1.5	0.8	18
W	8.5	18.4	16.0	
power/ time	(10-48)W/ 62 min	(15-55)W/ 70 min	(15-55)W/ 69 min	

Table A.3: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.20.

COMMENTS:

No discomfort in general, approximately 2.0 cm blister after the third treatment.

Probe (1): Spacing 0.5 cm
 Probe (2): Superficial, spacing 1.5 cm
 Probe (3): Spacing 1.0 cm
 Probes (1) and (3), 0.5 cm space

Figure A.3: Channel location in the tumor of patient no.20, tumors volume are 12.5 & 3.5 cm^3 .

Patient no.21					
Treatment no.	1	2	3	4	Channel no.
T.D	1.9	0.5	3.6	11.4	2
W	18.5	12.1	4.5	4.1	
T.D	0.4	5.6	7.1	12.2	3
W	19.1	5.8	3.7	3.1	
T.D	3.0	0.5	4.0	6.0	4
W	15.8	3.6	2.4	1.3	
T.D	3.1	0.3	9.8	10.2	5
W	2.9	2.1	2.0	2.7	
T.D	2.4	0.7	9.7	8.9	6
W	26.4	1.4	1.8	3.0	
T.D	0.7	1.7	7.4	7.3	7
W	20.3	0.8	2.1	1.5	
T.D	1.9	0.5	4.6	3.8	8
W	34.8	2.5	2.6	2.9	
T.D	0.6	1.0	2.4	0.0	21
W	25.6	2.6	1.3	1.6	
T.D	2.1	2.5	7.3	5.0	22
W	11.8	2.0	1.4	2.1	
T.D	0.8	3.7	66.1	45.5	23
W	15.6	2.2	1.7	2.6	
power/ time	(5-67)W/ 59 min	(8-73)W/ 70 min	(8-71)W/ 69 min	(8-75)W/ 70 min	

Table A.4: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.21.

COMMENTS:

Some discomfort during treatment 2, patient slept in treatment 3, fan on low in treatment 4.

Figure A.4: Channel location in the tumor of patient no.21, tumor volume is 12.0 cm^3 .

Patient no.22					
Treatment no.	1	2	3	4	Channel no.
T.D	20.7	0.6	2.1	3.7	0
W	1.3	1.1	7.3	5.4	
T.D	44.5	13.8	10.0	8.0	1
W	10.0	3.6	3.7	2.7	
T.D	22.0	19.0	37.8	18.6	2
W	1.8	2.7	3.0	2.5	
T.D	20.8	86.2	45.1	6.8	3
W	1.2	2.8	2.5	2.4	
T.D	37.1	32.0	21.8	6.6	4
W	1.7	2.5	2.7	2.4	
T.D	9.3	13.6	42.0	7.5	5
W	1.9	2.1	2.7	2.2	
T.D	2.8	18.0	60.0	4.4	6
W	2.0	2.1	2.6	2.2	
T.D	0.5	10.2	14.8	2.5	7
W	1.9	2.3	3.8	3.1	
T.D	0.7	1.6	5.6	0.6	8
W	2.7	2.2	5.6	3.9	
T.D	26.8	0.2	22.8	1.7	10
W	0.5	2.7	1.4	2.5	
T.D	254.8	107.4	346.0	341.0	11
W	1.4	2.4	1.9	2.4	
T.D	189.7	102.6	478.8	260.0	12
W	1.5	2.4	3.7	2.2	
T.D	401.3	194.5	138.9	110.4	13
W	2.0	3.3	6.7	3.0	

Patient no.22 cont.					
T.D	87.0	3.0	0.4	0.6	14
W	2.6	5.1	9.7	9.7	
T.D	33.0	9.5	22.3	0.0	16
W	0.7	1.7	1.7	-	
T.D	37.8	17.1	56.2	69.3	17
W	1.1	1.9	1.5	1.6	
T.D	77.4	16.8	115.3	71.5	18
W	1.2	1.7	1.8	1.6	
T.D	122.6	105.0	406.0	116.7	19
W	2.0	2.3	2.3	1.7	
T.D	70.0	98.0	190.0	101.6	20
W	2.4	2.5	2.7	2.0	
T.D	16.0	73.0	14.2	39.6	21
W	1.8	3.2	3.5	2.4	
T.D	29.3	9.0	4.1	5.0	22
W	2.6	3.4	5.6	4.1	
T.D	13.6	1.5	1.1	0.6	23
W	2.6	4.0	10.5	6.7	
power/ time	(10-34)W/ 59 min	(10-25)W/ 55 min	(10-22)W/ 68 min	(10-20)W/ 55 min	

Table A.5: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.22.

COMMENTS

Treatments 1 and 2 were excellent, in treatment 3 patient drifted in and out of sleep, with fluctuation in temperature, in treatment 4 patient was very uncomfortable.

Figure A.5: Channel location in the tumor of patient no.22, 3 nodules of volume 5.0, 1.8, and 0.2 cm^3 respectively.

Patient no.23					
Treatment no.	1	2	3	4	Channel no.
T.D	0.2	0.5	0.1	0.1	1
W	9.4	8.6	31.0	10.2	
T.D	1.4	6.0	1.0	2.0	2
W	4.6	5.8	8.5	6.3	
T.D	18.4	10.8	21.3	12.6	3
W	11.0	8.0	8.7	8.3	
T.D	1.0	0.2	0.3	0.5	4
W	10.4	6.7	7.7	10.9	
T.D	2.0	6.5	3.6	21.0	5
W	7.0	8.3	8.8	9.7	
T.D	1.3	2.1	1.3	9.6	6
W	9.2	12.3	8.0	8.1	
T.D	0.7	46.0	21.0	20.0	10
W	6.4	7.9	9.4	12.4	
T.D	9.5	13.0	56.0	28.5	11
W	9.2	5.7	8.4	13.3	
T.D	49.6	10.8	53.6	17.5	12
W	7.8	4.1	6.7	7.8	
T.D	26.0	1.5	25.0	6.0	13
W	6.1	7.2	5.1	5.2	
T.D	19.0	0.2	5.1	1.0	14
W	4.7	9.5	6.2	5.6	
T.D	2.3	0.0	0.4	0.0	15
W	5.8	-	5.0	9.1	
power time	(10-21)W/ 55 min	(10-19)W/ 69 min	(10-22)W/ 70 min	(10-24)W/ 60 min	

Table A 9: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.23.

COMMENTS:

Some discomfort during treatment 1 and 3.

Figure A.6: Channel location in the tumor of patient no.23, 4 nodules of volume: 1.5, 1.0, 0.5, and 0.25 cm³.

Patient no.24					
Treatment no.	1	2	3	4	Channel no.
T.D	0.3	0.5	0.4	0.7	2
W	5.6	3.2	12.3	18.2	
T.D	0.2	0.5	0.0	0.0	3
W	11.4	2.8	7.4	7.0	
T.D	0.0	0.0	0.0	0.0	4
W	16.9	2.6	15.6	35.0	
T.D	86.6	0.3	0.0	1.0	10
W	2.6	1.2	6.7	4.2	
T.D	3.3	5.7	39.0	70.5	11
W	8.9	0.8	2.8	2.9	
T.D	160.8	118.5	173.6	182.0	12
W	3.4	1.7	3.0	3.7	
T.D	0.0	48.7	53.4	25.2	13
W	9.8	0.8	5.9	5.7	
T.D	19.4	1.6	0.0	0.0	19
W	2.6	0.4	4.4	7.0	
T.D	3.3	19.1	10.5	0.0	20
W	3.3	0.8	2.4	2.3	
T.D	1.1	33.9	40.5	10.4	21
W	3.9	1.1	2.2	2.3	
T.D	1.0	24.5	47.8	32.0	22
W	6.2	1.0	2.5	2.7	
T.D	0.0	6.3	33.0	40.0	23
W	11.0	0.9	2.7	3.0	
power/ time	(8-18)W/ 63 min	(8-16)W/ 64 min	(10-13)W/ 69 min	(10-14)W/ 67 min	

Table A.7: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.24.

COMMENTS:

During treatments 1 and 3, patient slept.

Figure A.7: Channel location in the tumor of patient no.24, tumor volume is 21.6 cm³.

Patient no.25			
Treatment no.	1	2	Channel no.
T.D	0.5	0.2	1
W	2.2	6.5	
T.D	2.7	2.6	2
W	2.4	4.2	
T.D	1.6	6.2	3
W	2.7	5.1	
T.D	0.2	0.4	4
W	2.3	4.7	
T.D	1.4	0.3	7
W	1.6	3.9	
T.D	10.2	1.3	8
W	2.5	4.9	
T.D	14.2	22.2	9
W	2.8	7.2	
T.D	5.6	2.6	10
W	1.8	3.2	
T.D	0.3	0.2	15
W	2.7	12.1	
T.D	1.4	1.1	16
W	2.5	6.9	
T.D	7.0	7.7	17
W	2.3	4.5	

2 of/de 2

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

Patient no.25, cont.			
T.D	18.0	29.0	18
W	2.5	3.2	
T.D	17.0	28.0	19
W	3.0	2.2	
T.D	23.0	42.0	20
W	3.5	1.5	
T.D	4.2	4.0	21
W	2.7	4.6	
T.D	0.5	0.2	22
W	2.9	6.3	
power/ time	(10-22)W/ 73 min	(10-30)W/ 73 min	

Table A.8: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.25.

COMMENTS:

Patient slept during treatment 1, fan on low during treatment 2, simultaneous Chemo-infusion in both treatments.

Probe (1): Spacing 1.0 cm
 Probe (2): Spacing 1.0 cm
 Probe (3): Spacing 0.5 cm
 Probes (1) and (2): 2.0 cm space
 Probes (2) and (3): 1.5 cm space

Figure A.8: Channel location in the tumor of patient no.25, tumor volume is 120.0 cm³.

Patient no.26					
Treatment no.	1	2	3	4	Channel no.
T.D	1.0	0.7	0.6	0.5	3
W	8.7	7.4	7.5	4.2	
T.D	1.0	0.6	1.0	0.5	4
W	11.2	7.8	6.7	4.5	
T.D	0.0	0.0	13.4	0.2	10
W	12.8	7.7	8.7	4.9	
T.D	11.9	0.2	0.2	6.3	11
W	10.8	6.6	6.5	4.5	
T.D	299.6	888.0	4234.0	3083.0	12
W	6.5	5.7	5.7	3.8	
T.D	0.0	0.0	0.0	0.0	13
W	10.2	8.7	10.7	4.3	
T.D	0.0	0.0	0.0	0.0	14
W	6.4	14.4	10.0	5.8	
T.D	0.0	0.0	0.0	29.0	20
W	11.5	4.8	5.9	3.8	
T.D	0.0	0.0	0.0	6.3	21
W	8.2	4.6	6.1	3.8	
T.D	0.8	0.7	2.2	2.6	22
W	8.5	5.0	6.7	4.3	
T.D	2.0	0.4	3.6	6.0	23
W	9.4	6.5	5.8	4.2	
T.D	0.8	0.2	0.6	0.3	24
W	5.4	6.5	8.1	3.5	
power/ time	(10-30)W/ 71 min	(10-32)W/ 65 min	(10-42)W/ 69 min	(10-30)W/ 64 min	

Table A.9: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.26.

COMMENTS:

No discomfort during all the treatments.

Figure A.9: Channel location in the tumor of patient no.26, tumor volume is 5.5 cm³.

Patient no.27A					
Treatment no.	1	2	3	4	Channel no.
T.D	2.0	0.8	4.6	13.4	1
W	5.4	8.0	5.9	7.5	
T.D	1.1	3.2	1.3	5.2	4
W	4.1	6.8	5.8	7.0	
T.D	2.7	25.2	1.8	3.3	5
W	5.1	7.8	8.9	9.5	
T.D	36.7	48.4	21.0	30.0	10
W	4.1	6.5	8.2	8.2	
T.D	13.7	24.2	12.2	14.2	11
W	3.1	5.2	5.0	5.5	
T.D	1.7	1.5	3.4	2.1	15
W	3.3	4.9	5.1	5.1	
T.D	1.5	4.2	6.0	4.5	16
W	3.5	5.8	4.8	4.9	
T.D	1.9	4.2	8.1	6.2	17
W	4.1	6.0	5.0	5.7	
T.D	2.1	4.8	8.5	7.2	18
W	4.1	5.9	5.4	6.0	
T.D	3.7	8.2	10.3	13.1	19
W	4.5	6.0	5.5	5.2	
power/ time	(10-20)W/ 59 min	(10-30)W/ 70 min	(10-26)W/ 75 min	(10-35)W/ 70 min	

Table A.10: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.27 area A.

COMMENTS:

Two large blisters formed after first treatment, and air used to cool the surface.

Figure A.10: Channel location in the tumor of patient no.27 area A, 6 nodules of volume: 2.8, 1.8, 1.2, 1.0, 1.0, 0.3 cm³.

Patient no.27B					
Treatment no.	1	2	3	4	Channel no.
T.D	5.7	5.8	12.0	15.0	2
W	3.0	3.5	2.7	3.3	
T.D	30.5	11.0	27.0	49.0	3
W	4.0	3.9	3.3	3.6	
T.D	25.0	3.0	2.5	6.0	4
W	5.7	4.7	4.0	4.3	
T.D	224.0	26.0	11.0	27.0	5
W	5.6	5.4	4.5	4.6	
T.D	1.0	1.5	8.0	18.0	10
W	6.7	6.9	12.0	6.6	
T.D	0.5	0.3	4.6	4.0	11
W	6.2	7.3	7.5	4.6	
T.D	0.5	0.5	1.0	2.3	12
W	4.3	5.2	5.5	3.7	
T.D	2.3	2.0	5.0	16.0	13
W	3.8	4.2	4.0	3.4	
T.D	7.7	3.0	19.0	37.0	14
W	4.2	4.8	4.2	3.5	
T.D	11.0	4.4	18.0	36.0	15
W	4.7	4.8	4.4	3.4	
T.D	18.0	4.0	16.0	20.0	16
W	4.5	5.2	3.3	3.7	
T.D	52.0	19.0	28.0	50.0	17
W	4.2	4.8	3.3	3.5	
T.D	93.0	13.0	38.0	37.0	18
W	5.2	4.7	2.9	3.6	
T.D	93.0	18.0	30.0	41.0	19
W	7.7	5.4	2.5	3.7	
power/ time	(10-20)W/ 60 min	(10-25)W/ 70 min	(10-23)W/ 70 min	(10-32)W/ 68 min	

Table A.11: Thermal Dose T.D(eq-min at 43°) and Blood Perfusion Rate W(ml/ml/min) of patient no.27 area B.

COMMENTS:

Good treatments in general.

Figure A.11: Channel location in the tumor of patient no.27 area B, 3 nodules of volume: 1.3, 1.2, and 1.2 cm³.

Patient no.28

Treatment no.	1	2	Channel no.
T.D	0.0	0.0	1
W	6.6	5.0	
T.D	0.8	0.6	2
W	5.3	4.6	
T.D	0.0	0.0	3
W	9.9	4.4	
T.D	0.0	0.0	4
W	3.1	2.3	
T.D	0.0	0.0	5
W	2.6	1.9	
T.D	0.0	0.0	7
W	5.2	8.5	
T.D	0.0	0.0	10
W	13.5	22.3	
T.D	0.8	0.2	11
W	14.8	11.1	
T.D	1.4	0.5	12
W	10.2	5.6	
T.D	11.3	6.4	13
W	7.9	10.6	
T.D	11.0	4.7	14
W	7.2	9.5	

Patient no.28, cont.			
T.D	5.7	3.3	15
W	8.2	8.0	
T.D	8.8	7.0	16
W	7.5	6.7	
T.D	21.2	27.1	17
W	6.4	5.3	
T.D	41.8	47.4	18
W	6.5	5.9	
T.D	28.2	2.1	21
W	11.8	6.3	
T.D	45.5	47.2	22
W	9.5	4.3	
T.D	56.0	128.0	23
W	7.5	3.9	
T.D	3.0	4.6	24
W	8.0	5.6	
T.D	0.8	0.5	25
W	7.0	7.7	
power/ time	(10-48)W/ 74 min	(10-36)W/ 74 min	

Table A.12: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.28.

COMMENTS:

Good treatments, no discomfort.

Probe (1): Spacing 1.0 cm
 Probe (2): Spacing 0.5 cm
 Probe (3): Spacing 1.0 cm
 1.5 cm space between
 probes

Figure A.12: Channel location in the tumor of patient no. 28, tumor volume is 26.0 cm^3 .

Patient no.29			
Treatment no.	1	2	Channel no.
T.D	0.0	0.0	2
W	15.2	10.7	
T.D	0.0	0.0	3
W	10.0	11.0	
T.D	7.8	1.7	4
W	6.4	10.1	
T.D	25.6	7.9	5
W	4.3	8.0	
T.D	30.2	8.5	7
W	8.2	9.6	
T.D	0.0	0.0	12
W	6.7	25.0	
T.D	0.0	0.0	13
W	8.0	10.3	
T.D	0.0	0.0	14
W	9.2	10.8	
T.D	0.0	0.0	15
W	7.6	10.4	
T.D	1.6	5.5	16
W	7.5	9.6	
T.D	3.4	24.3	17
W	5.9	8.7	
T.D	20.5	37.4	18
W	5.6	8.4	
T.D	65.0	38	19
W	5.7	11.2	
power/ time	(10-16)W/ 67 min	(10-25)W/ 71 min	

Table A.13: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.29.

COMMENTS:

Large blister formed after first treatment.

Figure A.13: Channel location in the tumor of patient no.29, tumor volume is 4.0 cm^3 .

Patient no.30					
Treatment no.	1	2	3	4	Channel no.
T.D	11.3	8.4	18.5	18.0	1
W	8.2	6.8	11.7	11.3	
T.D	28.1	10.8	0.8	4.0	2
W	5.1	4.8	8.0	22.8	
T.D	75.0	25.0	1.3	5.7	3
W	3.0	5.1	11.0	14.4	
T.D	2.3	5.5	0.3	1.5	12
W	10.0	2.9	5.0	17.0	
T.D	1.8	8.5	1.0	0.5	13
W	10.4	2.7	12.0	11.5	
T.D	6.2	39.0	1.5	2.6	14
W	10.5	2.9	6.7	7.7	
T.D	5.0	13.0	0.7	6.8	15
W	16.2	3.5	9.6	8.9	
T.D	2.6	3.0	0.2	4.2	16
W	10.5	5.3	10.0	7.4	
T.D	1.3	1.2	0.0	2.0	17
W	8.6	7.9	16.6	7.4	
T.D	5.6	1.8	12.2	2.0	22
W	6.4	6.1	10.0	7.2	
T.D	6.0	2.0	5.2	1.0	23
W	9.1	3.0	9.4	8.4	
T.D	4.5	1.0	1.1	3.5	24
W	8.3	3.5	4.8	9.5	
power/ time	(10-45)W/ 70 min	(10-32)W/ 59 min	(10-40)W/ 67 min	(10-45)W/ 70 min	

Table A.14: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.30.

COMMENTS:

Fan used during treatments 1, 2, and 4, with some adjustment to the applicator during the first treatment. Patient was very uncomfortable during the treatment course.

Figure A.14: Channel location in the tumor of patient no.30, tumor volume is 20.0 cm^3 .

Patient no.31			
Treatment no.	1	2	Channel no.
T.D	5.0	3.2	3
W	2.5	1.6	
T.D	14.4	17.4	4
W	2.5	1.6	
T.D	9.6	9.0	5
W	2.8	2.0	
T.D	10.4	2.4	9
W	5.1	4.0	
T.D	11.2	2.8	10
W	4.7	3.5	
T.D	13.1	6.6	11
W	3.7	3.2	
T.D	22.1	2.3	12
W	3.7	2.8	
T.D	3.7	0.6	13
W	4.2	2.3	
T.D	1.6	1.4	14
W	3.6	3.2	
T.D	3.7	3.7	15
W	4.6	3.4	
T.D	8.7	5.0	16
W	4.7	2.7	
T.D	9.0	5.7	17
W	4.6	1.8	
T.D	4.1	20.0	18
W	4.9	1.5	

Patient no.31, cont.			
T.D	7.0	81.0	19
W	5.0	1.4	
T.D	18.0	1.2	20
W	4.5	2.6	
T.D	33.0	3.4	21
W	4.7	4.9	
T.D	27.0	5.0	22
W	4.6	5.1	
T.D	6.6	4.5	23
W	7.2	2.8	
T.D	7.6	20.0	24
W	8.0	1.0	
T.D	1.5	16.2	25
W	8.0	0.6	
T.D	3.8	87.0	26
W	5.9	1.2	
T.D	2.7	66.0	27
W	4.8	0.8	
power/ time	(10-30)W/ 73 min	(10-29)W/ 67 min	

Table A.15: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.31.

COMMENTS:

Air used after 30 min from starting the first treatment.

Figure A.15: Channel location in the tumor of patient no.31, tumor volume is 6.0 cm^3 .

Patient no.32					
Treatment no.	1	2	3	4	Channel no.
T.D	0.5	0.2	0.1	0.0	0
W	5.4	6.5	8.9	-	
T.D	1.4	0.4	0.3	0.1	1
W	5.2	3.3	5.7	-	
T.D	11.0	3.1	6.2	4.4	2
W	7.4	3.9	5.0	14.5	
T.D	58.0	10.0	23.0	5.0	3
W	8.0	5.0	8.1	15.0	
T.D	79.0	28.0	35.0	28.0	4
W	9.0	7.5	12.5	11.7	
T.D	105.0	75.0	41.0	36.0	5
W	11.3	8.4	10.1	20.8	
T.D	1.4	4.7	5.5	1.8	11
W	7.7	6.2	12.4	19.9	
T.D	9.4	4.7	2.7	1.2	12
W	6.9	4.7	6.2	10.2	
T.D	9.2	1.4	1.6	0.3	13
W	5.3	4.5	5.9	25.3	
T.D	3.2	2.7	11.4	3.4	14
W	6.1	4.2	5.2	21.2	
T.D	11.2	18.2	57.0	72.0	15
W	6.1	4.4	5.9	18.5	

Patient no.32, cont.					
T.D	45.0	12.0	9.5	8.5	16
W	7.0	5.3	10.2	20.4	
T.D	19.0	11.0	16.0	7.0	17
W	9.9	5.7	10.8	21.4	
T.D	31.0	5.0	1.1	0.5	18
W	10.1	7.9	12.0	29.4	
T.D	241.0	89.0	94.0	146.0	21
W	5.8	4.2	4.4	11.2	
T.D	67.0	15.0	26.0	33.0	22
W	3.6	3.6	3.9	10.9	
T.D	29.0	9.0	12.0	4.0	23
W	3.7	3.4	4.5	15.4	
power/ time	(10-32)W/ 72 min	(11-32)W/ 70 min	(11-32)W/ 70 min	(13-37)W/ 75 min	

Table A.16: Thermal Dose T.D(eq-min at 43°C) and Blood Perfusion Rate W(ml/ml/min) of patient no.32.

COMMENTS:

In treatment 1: Sudden rise in temperature at 62 min, therefore the power was dropped 20 Watts, a small blister was seen after the treatment. In the rest of treatments no discomfort was noticed.

Probe (1): Spacing 1.0 cm
 Probe (2): Spacing 0.5 cm
 Probe (3): Spacing 1.0 cm
 1.5 cm space between probes

Figure A.16: Channel location in the tumor of patient no.32, tumor volume is 20.0 cm^3 .

76-1263

08/11/88 11:20 C:\PAT08X1.MDF
RECTANG. APPLICATOR

Figure A.17: Patients temperature profiles.
Data from patient no.8.

2ND TMT AFTER REMOVAL OF IMPLANT

06/16/89 15.00 C: PAT29X02.MDF

NO DISCOMFORT; CHANNELS 4,5 UNDER TUMOUR 19 UNDER BLISTER

FigureA.18: A continuous increase in power to maintain the therapeutic temperature constant. Data from patient no.29.

09/30/88 10:32 C. PAT22X02.MDF

TEMP INCREASE AT 24 MIN OCCURED WITH APOWER INCREASE OF ONLY 2 W

Figure A.19: A variation in power due to a changing in blood flow.
Data from patient no.22.

Appendix B

Computer program

```
c      This program is designed to take sequential temperature values
c      and calculate the accumulated Equivalent-minute at the
c      reference temperature (43°C).
c      The program is written in Fortran 77, and was run on a
c      VAX station 2000.
c      TEMP = Temperature data
c      T43 = Equivalent-minute at reference temperature
c      43°C
c      TREF = Reference temperature
c      TBREAK= Break temperature, chosen to be 43°C
c      TSUM = Equivalent time at break temperature
c      RABOVE = R value above the break temperature, equal 2
c      RBELOW = R value below the break temperature (4-8)
c      SUMRF = Equivalent time function
c      TAVE = Average temperature during Delta t

      REAL TIME(144),TEMP(144),TREF,TBREAK,TSUM
      REAL T43,RABOVE,RBELOW,TAVE,SUMRF
      COMMON /PRESET/ TREF,TBREAK,RABOVE,RBELOW
      DATA TREF/43.0/,RABOVE/2.0/,TBREAK/43.0/
      WRITE(10,20)
20      FORMAT(8X,' PAT18X01 CH 1 ',/)
```

```

RBELOW=4.0
DO 1 I=1,5
CALL DATRD(TIME,TEMP)
T43=SUMRF(TIME,TEMP)
WRITE(10,1060)RABOVE,RBELOW
WRITE(10,1050)TREF,TBREAK
WRITE(10,1080)T43
1060  FORMAT(2X,/, ' RABOVE=',G10.2,5X,'RBELOW=',G10.2)
1050  FORMAT(2X,/, ' TREF=',F10.2,7X,'TBREAK=',F10.2)
1080  FORMAT(/,24X,'T43=',F14.8)
RBELOW=RBELOW+1
PRINT *, 'T43=',T43
1  CONTINUE
STOP
END

```

```

FUNCTION SUMRF(TIME,TEMP)
c  This function calculates the equivalent time at the
c  reference temperature
REAL TIME(144),TEMP(144),TREF,TBREAK,TSUM,RABOVE
REAL RBELOW,TAVE,DELTAT
COMMON /PRESET/ TREF,TBREAK,RABOVE,RBELOW
c  CALCULATE EQUIVALENT TIME
TSUM=0.0
DO 100 J=1,143
R=RABOVE
DELTAT=ABS(TIME(J+1)-TIME(J))
TAVE=ABS(TEMP(J)+TEMP(J+1))/2.0
IF(TAVE.LE.TBREAK)R=RBELOW
TSUM=TSUM+DELTAT*R**(TAVE-TBREAK)
100  CONTINUE
R=RABOVE
IF(TREF.LT.TBREAK)R=RBELOW
SUMRF=TSUM*R**(TBREAK-TREF)
RETURN
END

```

```
c      This subroutine reads the temperature data file;
c      FILNAM.DAT
      SUBROUTINE DATRD(TIME,TEMP)
      DIMENSION TIME(144),TEMP(144)
      OPEN(UNIT=4,NAME='FILNAM.DAT',STATUS='OLD')
      READ(4,100,END=98)(TIME(I),I=1,144)
100    FORMAT(G7.2)
98     CLOSE(UNIT=4)
      OPEN(UNIT=4,NAME='FILNAM.DAT',STATUS='OLD')
c      READING FROM CHANNELS
      READ(4,110,END=99)(TEMP(I),I=1,144)
110    FORMAT(140X,G7.2)
99     CLOSE(UNIT=4)
      RETURN
      END
```

Appendix C

Human statistics

Patient no.	No. of data points	Average B.P.R	Median B.P.R	S.D	Range
18	19	1.4	1.3	0.64	0.3-3.1
19	7	3.0	3.1	0.38	2.6-3.6
20	11	6.5	6.1	1.26	4.3-8.5
21	7	4.0	2.1	4.27	0.8-12.1
22	8	2.9	2.8	1.2	1.7-5.1
23	3	7.9	8.6	2.1	5.8-9.5
24	10	1.6	1.5	0.76	0.8-3.2
25	14	5.4	4.8	2.4	3.2-12.1
26	8	6.5	6.5	1.5	4.6-8.7
27A	9	6.4	6.2	0.9	5.2-8.0
27B	6	4.6	4.7	0.8	3.5-5.4
28	5	4.8	4.4	3.9	1.9-10.6
29	3	9.2	8.0	1.2	8.0-10.1
30	10	4.4	4.8	1.64	2.7-7.9
31	11	2.3	2.1	0.6	1.4-3.4
32	9	4.5	4.5	0.9	3.6-6.4

Table C.1: Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statistics, of the second treatment.

Patient no.	No. of data points	Average B.P.R	Median B.P.R	S.D	Range
19	7	4.7	4.8	0.87	3.3-5.6
20	11	11.0	10.5	3.2	7.7-18.4
21	7	2.5	2.1	1.17	1.4-4.5
22	8	4.4	3.7	2.79	1.8-9.7
23	3	14.7	8.0	14.3	6.2-31
24	10	6.1	4.5	4.2	2.2-15.6
26	8	7.0	6.5	1.76	5.7-10.7
27A	9	6.1	5.7	1.37	4.8-8.9
27B	6	4.0	4.2	0.74	2.7-4.5
30	10	9.8	9.5	2.2	5.0-12.0
32	9	6.5	5.5	2.8	3.9-12.4

Table C.2: Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statistics, of the third treatment.

Patient no.	No. of data points	Average B.P.R	Median B.P.R	S.D	Range
19	7	4.0	4.2	0.56	3.2-4.7
20	11	18.4	16.1	5.3	11.4-29.0
21	7	2.7	3.0	1.06	1.3-4.1
22	8	3.6	3.0	2.8	1.6-9.7
23	3	8.0	8.1	2.66	5.6-10.2
24	10	8.4	4.9	10.3	2.3-35.0
26	8	4.2	4.2	0.25	3.8-4.5
27A	9	6.6	6.0	1.5	4.9-9.5
27B	6	3.8	3.5	0.5	3.3-4.6
30	10	11.3	10.2	4.9	7.2-22.8
32	9	16.9	16.0	4.97	10.4-25.3

Table C.3: Human tumor Blood Perfusion Rate (B.P.R)(ml/ml/min) statistics, of the fourth treatment.

Patient no.	Treatment 1	Treatment 2	Treatment 3	Treatment 4
18	4.2	9.2	-	-
19	14.5	22.5	24.5	37.5
20	-	36.1	41.3	34.1
21	29.3	7.0	18.3	13.9
22	72.3	44.5	92.5	65.3
23	13.1	12.5	23.4	14.7
24	45.7	32.2	56.9	60.1
25	9.1	14.5	-	-
26	79	127	532	621
27A	6.8	13.8	7.7	10.0
27B	51.1	9.3	16.9	25.7
28	21.5	28.0	-	-
29	22.0	18.0	-	-
30	12.5	10.0	5.2	4.7
31	10.2	17.2	-	-
32	45.0	19.0	23.0	27.0

Table C.4: Patients tumor average Thermal Dose (equivalent-minutes at 43°C).

References

- [1] R. Jain, Temperature distributions in normal and neoplastic tissues during normothermia and hyperthermia, *Annals New York Academy of Sciences*, **335**:48-63 (1980)
- [2] E. Cravalho et al., The application of the Bioheat Equation to the design of thermal protocols for local hyperthermia, *Annals New York Academy of Sciences*, **335**:86-98 (1980)
- [3] R. Eberhart et al., Thermal dilution methods: estimation of tissue blood flow and metabolism, *Annals New York Academy of Sciences*, **335**:107-132 (1980)
- [4] W. Wulff, Discussion paper: alternatives to the Bioheat Transfer Equation, *Annals New York Academy Of Sciences*, **335**:151-154 (1980)
- [5] K. Henle et al., Time-Temperature relationships for heat-induced killing of mammalian cells, *Annals New York Academy of Sciences*, **335**:234-253 (1980)
- [6] G. Hahn et al., Some heat transfer problems associated with heating by ultrasound, microwaves, or radio frequency, *Annals New York Academy of Sciences*, **335**:327-346 (1980)
- [7] E. Hahn et al., Clinical observations, *Annals New York Academy of Sciences*, **335**:347-352 (1980)
- [8] G.P. Raaphorst, Thermal radiosensitization in vitro, *Hyperthermia and oncology*. Editor Muneyasu Urano, Vol 2 (1990).

- [9] P.B. Dunscombe et al., Heat production in microwave-irradiated thermocouples, *Medical Physics*, Vol 13, No. 4, 457-462 (1986)
- [10] F. Dietzel, Tumorthrapy with Hyperthermia, *Cancer Research*, Vol. 86, 177-187 (1983)
- [11] H. Eddy et al., Tumor microvascular response, *Natl. Cancer Inst. Monogr*, 61:225-229 (1982)
- [12] C. Streffer et al., The biological basis for tumor therapy by hyperthermia and radiation, *Cancer research*, Vol. 104, 24-31 (1987)
- [13] F. Waterman, The response of thermometer probes inserted into catheters, *Medical Physics*, Vol. 12, 368-372 (1985)
- [14] E. Jones et al., Thermal enhancement of low dose rate irradiation in a murine tumour system, *Int. J. Hyperthermia*, Vol. 5, 509-523 (1989)
- [15] M. Engler et al., Stability of temperatures during hyperthermia treatments, *Int. J. Hyperthermia*, Vol. 5, No. 1, 59-67 (1989)
- [16] G. Hahn, Hyperthermia and cancer, 36-53 (1982)
- [17] M. Astrahan et al., Microwave applicator for transurethral hyperthermia of benign prostatic hyperplasia, *Int. J. Hyperthermia*, Vol. 5, No. 5, 283-296 (1989)
- [18] P. Stauffer et al., Comparative thermal dosimetry of interstitial microwave and radiofrequency-LCF hyperthermia, *Int. J. Hyperthermia*, Vol. 5, No. 3, 307-318 (1989)
- [19] B. Partington et al., Temperature distributions in normal tissue heated by ferromagnetic needles, *Int. J. Hyperthermia*, Vol. 5, No. 3, 319-327 (1989)
- [20] S. Hill, Reduced thermal sensitivity of the vasculature in a slowly growing tumour, *Int. J. Hyperthermia*, Vol. 5, No. 3, 359-370 (1989)
- [21] P. Vaupel, Response of tumor red blood cell flux to hyperthermia and/or hyperglycaemia, *Int. J. Hyperthermia*, Vol. 5, No. 2, 199-210 (1989)

- [22] M. Dewhirst, Biological rationale and clinical overview of hyperthermia, *Advances in Bioengineering*, 63-65 (1985)
- [23] J. Rhee, Changes in acidity of mouse tumor by hyperthermia, *Int. J. Radiation Oncology Biol. Phys.*, Vol. 10, 393-399 (1984)
- [24] B. Emami et al., Physiological mechanisms in hyperthermia, *Int. J. Radiation Oncology Biol. Phys.*, Vol. 10, 289-295 (1984)
- [25] C. Perez et al., Clinical results of irradiation combined with local hyperthermia, *Cancer*, November 1, 1597-1603 (1983)
- [26] Hyperthermia treatment planning, *American Association of Physicists in Medicine*, AAPM Report No.27
- [27] M. Saposink et al., Practical thermal dosimetry, *Int. J. Radiation Oncology Biolog. Phys.*, Vol. 11, 555-560 (1985)
- [28] P. Sijens et al., Phosphorus NMR study of the response of a murine tumor to hyperthermia, *Int. J. Hyperthermia*, Vol. 5, No. 3, 351-357 (1989)
- [29] D. Thrall et al., Whole body hyperthermia in dogs, *Int. J. Hyperthermia*, Vol. 5, NO. 2, 137-143 (1989)
- [30] R. Levin et al., A heat and mass transfer model for computing thermal dose during hyperthermic treatment of extremities, *Advances in Bioengineering*, 13-15 (1985)
- [31] C. Perez et al., Thermal dose expression in clinical hyperthermia and correlation with tumor response, *Cancer research (Suppl.)*, 44:4818-4825 (1984)
- [32] F. Gibbs, Regional hyperthermia, *Cancer research (Suppl.)*, 44:4765-4770 (1984)
- [33] J. Oleson, Heat delivery session, *Cancer research (Suppl.)*, 44:4771-4779 (1984)
- [34] J. Strohbehn, Calculation of absorbed power in tissue for various hyperthermia devices, *Cancer Research (Suppl.)*, 44:4781-4787 (1984)

- [35] B. Davis et al., A theoretical study of rapid hyperthermia by scanned, focused ultrasound, *J. of Biomedical Engineering*, 126:51-59 (1990)
- [36] S. Sapareto et al., Thermal dose determination in cancer therapy, *Int. J. Radiation Oncology Biol. Phys.*, 10:787-800 (1984)
- [37] W. Dewey et al., Cellular responses to combinations of hyperthermia and radiation, *Radiology*, 123:463-474 (1977)
- [38] S. Sapareto, Thermal isoeffect dose, *Int. J. Hyperthermia*, Vol. 3, No. 4, 297-305 (1987)
- [39] V. Sathiascelan et al., A clinical microwave hyperthermia system with multipoint real-time thermal dosimetry, *The British Journal of Radiology*, 58:1187-1195 (1985)
- [40] G.P. Raaphorst, Thermal dose considerations: Letter to the editor. Inpress, *Int. J. Hyperthermia*, 1991.
- [41] W. Dewey, Mechanisms of heat damage, March 1984
- [42] G.P. Raaphorst, Fundamental aspects of hyperthermic biology, prepared as chapter 2 in, An introduction to the practical aspects of clinical hyperthermia. Editors, S.B. Field and J.W. Hand
- [43] F. Waterman et al., Response of human tumor blood flow to local hyperthermia, *Int. J. Radiation Oncology Biol. Phys.*, 13:75-82 (1987)
- [44] M. Knudsen, Estimation of tissue blood flow from hyperthermia treatment data, *Int. J. Hyperthermia*, Vol. 5, No. 5, 653-661 (1989)
- [45] J. Chato, Heat transfer to blood vessels, *Journal of Biomechanical Engineering*, 102:110-118 (1980)
- [46] C. Song et al., Implication of blood flow in hyperthermic treatment of tumors, *IEEE Transactions on Biomedical Engineering*, Vol. BME-31, No. 1, 9-16 (1984)
- [47] S. Clegg et al., Towards the estimation of three-dimensional temperature fields from noisy temperature measurements during hyperthermia, *Int. J. Hyperthermia*, Vol. 5, No. 4, 467-484 (1989)

- [48] K. Hynynen et al., The effect of blood perfusion rate on the temperature distributions, *Int. J. Hyperthermia*, Vol. 5, No. 4, 485-497 (1989)
- [49] H. Frederick Bowman et al., Measurements, Theory, and application of thermal properties of biomaterials, *J. Biomechanical Engineer*, 43-81 (1975)
- [50] B. Lyons et al., Heat loss and blood flow during hyperthermia in normal canine brain, *Int. J. Hyperthermia*, Vol. 5, No. 2, 225-247 (1989)
- [51] T. Samrlski et al., Heat loss and blood flow: Mathematical model, *Int. J. Hyperthermia*, Vol. 5, No. 2, 249-263 (1989)
- [52] M. Maeta et al., The effect of angiotensin II on blood flow in tumors during localized hyperthermia, *Int. J. Hyperthermia*, Vol. 5, No. 2, 191-197 (1989)
- [53] F. Waterman et al., Determination of the transport of thermal energy by conduction in perfused tissue, *Heat transfer in Biomechanical Engineer*, 37-43 (1987)
- [54] W. Newman et al., Tissue thermal properties, *J. Biomechanical Engineer*, 45-50 (1987)
- [55] W. Newman et al., In-vitro measurements of low-level tissue blood flow, *J. Biomechanical Engineer*, 51-56 (1987)
- [56] C. Madhusudana et al., Thermal conductance in bolted and riveted joints, *J. Biomechanical Engineer*, 57-67 (1987)
- [57] H. Arkin et al., Local thermal conductivity and blood perfusion, *J. Biomechanical Engineer*, 108:208-214 (1986)
- [58] K. Almenas et al., Tissue property measurements, *J. Biomechanical Engineer*, 39-44 (1988)
- [59] J. Lagendijk, The influence of blood flow in large vessels on the temperature distribution in hyperthermia, *Phys. Med. Biol.*, Vol. 27, No. 1, 17-23 (1982)

- [60] S. Clegg et al., Three-dimensional temperature distributions during hyperthermia experiments, *J. Biomedical Engineering*, 37-44 (1990)
- [61] S. Afuwape et al., Thermal distribution, *J. Biomedical Engineering*, 126:67-71 (1990)
- [62] G. Trezek et al., Transient temperature fields, *Biomedical Engineering*, Vol. BME-17, No. 4, 281-285 (1970)
- [63] R. Jain et al., Heat transfer in tumors, *Chem. Eng. Commun.*, 4, 95-118 (1980)
- [64] J.C. Acker et al., Blood perfusion measurements, *Int. J. Hyperthermia*, Vol. 6, No. 2, 287-304 (1990)
- [65] R.B. Roemer et al., Applications of bioheat transfer simulations in hyperthermia, *Cancer research*, 44:4788-4798 (1984)
- [66] C.W. Song, Effect of local hyperthermia on blood flow and microenvironment, *Cancer research (Suppl.)*, 44:4721-4739 (1984)
- [67] T. Samulski et al., Thermal washout rate, *Int. J. Radiation Oncology Biol. Phys.*, 13:907-916 (1987)
- [68] T. Dudar et al., Differential response of normal and tumor microcirculation to hyperthermia, *Cancer research*, 44:605-612 (1984)
- [69] A. Olch et al., Blood flow in human tumors, *Journal of Surgical Oncology*, 23:125-132 (1983)
- [70] S. Clegg et al., Tumor temperature distribution, *Advances in Bioengineering*, 147-150 (1983)
- [71] H. Reinhold et al., Tumor microcirculation, *Int. J. Hyperthermia*, Vol. 2, No. 2, 111-137 (1986)
- [72] S. Hume et al., Blood flow during treatment, *British Journal of Radiology*, 52:219-222 (1979)
- [73] T. Morimoto et al., Changes in vascular compliance during hyperthermia, *J. therm. Biol.*, Vol. 9, No. 1/2, 149-151 (1984)

- [74] C. Gordon et al., Temperature regulation in the mouse, *Health Physics*, Vol. 50, No. 6, 781-787 (1986)
- [75] J. Peck et al., Capillary blood flow in murine tumors, *Radiation research*, 96:65-81 (1983)
- [76] A.J. Milligan et al., Prediction of blood flow from thermal clearance, *Int. J. Radiation Oncology Biol. Phys.*, 9:1335-1343 (1983)
- [77] J. Meyer, Thermotolerance, *Radiation Oncology Biol. Phys.*, 11, No. 5:973-981 (1985)
- [78] J. Lagendijk et al., A three-dimensional description of heating patterns in vascularised tissues, *Phy. Med. Biol.*, Vol. 29, No. 5, 495-507 (1984)
- [79] S. Weinbaum et al., A new simplified bioheat equation, *J. Biomechanical Engineering*, 107:131-138 (1985)
- [80] R. Roemer et al., Temperature measurements, *Int. J. Radiation Oncology Biol. Phys.*, 11:1539-1550 (1985)
- [81] T. Sandhu, Measurement of blood flow using temperature decay: Effect of Thermal conduction, *Int. J. Radiation Oncology Biol. Phys.*, 12:373-378 (1986)
- [82] W. Wulff, The energy conservation equation for living tissue, *IEEE Transactions on Biomedical Engineering*, pp 3-4 (1974)
- [83] S. Garnis-Jones et al., Complications of microwave hyperthermia treatment of psoriasis, *J. American Academy of Dermatology*, 22:651-653 (1990)
- [84] G. Hahn, Hyperthermia and cancer, 1982
- [85] E. Kano, Current research in Hyperthermia Oncology, 1988
- [86] L. Anghileni et al., Hyperthermia in cancer treatment, Vol. II (1986)
- [87] N. Hornback et al., Hyperthermia and cancer, Vol. I (1984)
- [88] F. Storm, Hyperthermia in cancer therapy, 1983

- [89] U. Akyurekli, Simulation of ultrasound hyperthermia, M.Sc Thesis (1988)
- [90] f. Gullino et al., Relationship between temperature and blood supply, *J. Natl. Cancer Inst.*, **60**:835-847 (1978)
- [91] R. Emmami et al., Physiological effects of hyperthermia, *Radiology*, **137**:805-809 (1980)
- [92] K. Bauer et al., *Radiation research*, **78**:251-263 (1979)
- [93] R. Roti et al., *Rad. Res*, **78**:522-531 (1979)
- [94] O. Nielsen et al., *Cancer Research*, **39**:2772-2778 (1979)
- [95] S. Morris et al., The relationship between heating time and temperature, *Radiotherapy and Oncology*, **1**:179-186 (1983)
- [96] S. Sapareto et al., Hyperthermia effects on survival and progression of CHO cells, *Cancer Res.*, **38**:393-400 (1978)
- [97] L. Gerweck et al., Influences of pH on the response of cells to single and split doses of hyperthermia, *Cancer Res.*, **40**:4019-4024 (1980)
- [98] L. Rice et al., The kinetics of thermotolerance in the mouse foot, *Rad. Res.*, **89**:291-297 (1982)
- [99] G. Li et al., Adaptation to different growth temperatures modifies some mammalian cell survival responses, *Exp. Cell Res.*, **128**:475-485 (1980)
- [100] L. Law et al., The response of the mouse ear to heat applied alone or combined with X-rays, *Brit. J. Radiol.*, **51**:132-138 (1978)
- [101] R. Myers et al., The relationship between heating time and temperature by combined hyperthermia and X-radiation, *Int. J. Radiat. Biol.*, **38**:373-382 (1980)
- [102] J. Mantyla et al., Regional blood flow in human tumors, *Brit. J. Radiol.*, **49**:335-338 (1979)
- [103] M. Dewhirst et al., Heterogeneity in tumor microvascular response to radiation, *Int. J. Rad. Oncology Biol. Phys.*, **3**:212-230 (1989)

- [104] H.H. Pennes, Analysis of tissue and arterial blood temperature in the resting human forearm, *J. Appl. Physiol.*, 1:93-122 (1948)

END

04/03/92

FIN