The Study of Standardization of Temperature Distribution of Interstitial Hyperthermia

—In Phantoms and Living cat's brain tissue (Normal Tissue)—

Kyoung Hwan Koh, M.D., Chul Koo Cho, M.D., Young Hwan Park, M.D.
Woo Yoon Park, M.D., Seong Yul Yoo, M.D., Jong Hyun Kim, M.D.*
and Seung Hoon Lee, M.D.*

Department of Therapeutic Radiology and Neurosurgery, Korea Cancer Center Hospital, KAERI*

The ultimate objective of our experiment is to obtain the precise distribution of temperature in malignant tumors occurring in cerebral parenchyme of human beings when we will carry out interstitial hyperthermia in the near future. To achieve this purpose, first of all, it is necessary to make an attempt at performing interstitial hyperthermia in vivo under the similar condition of human beings. Therefore, we chose cats as materials much alike tissue characteristics of human beings. Moreover, it is also necessary to get the basic data from dynamic phantom in order to standardize and compare results obtained from interstitial hyperthermia carried out in cats.

By having performed these experiments we got the following results.

1) On doing interstitial hyperthermia with 915 MHz microwave, the possible treated volume was 2 cm by 2 cm by 6 cm according to 50% specific absorption rate (SAR).

2) The distribution of temperature within non-circulated static phantom was much the same as power density in air, but we observed that the temperature, within 5~10 minutes, rose to more higher than 55℃ not measured with Ga-As fiberoptic thermistor which was not impeded by microwave after performing interstitial hyperthermia.

3) Within dynamic phantom in which normal saline was circulating, temperature reached steady state which was maintained for more than 45 minutes through transit period in 5 minutes after starting interstitial hyperthermia.

4) When we interrupted circulation in the dynamic phantom, we observed that temperature rose to the same level as in the static phantom.

5) We could carry out interstitial hyperthermia safely when we used the generating power below 5 watts. Abrupt interruption of circulation caused a rapid increase in temperature. Times taking to rise to maximum 55℃ were 15.2 minutes (SE 0.4), 9.7 minutes (SE 0.3), and 6.3 minutes (SE 0.4) respectively with generating powers of 5, 10, and 15 watts.

Key Words: Interstitial hypethermia, Dynamic and static phantoms, Circulation, Living cat's brain tissue (normal tissue), Microwave applicator

INTRODUCTION

Recently there has been a growing interest in the use of hyperthermia as a new modality for cancer therapy. It has been demonstrated that hyperthermia can be effective and safe method in the treatement of locally-advanced malignant tumors, when it is used alone or combined with radiation therapy and/or chemotherapy[1~8].

In contrast to a malignant tumors, there is a major difficulty in hyperthermia induction, great effectiveness of hyperthermia in controlling the especially when its heat is delivered with external applicators. Hyperthermia with external applicators makes it easy to treat the skin cancer or cancer located at the area of 2-5 cm below the skin. As a result, burn and skin necrosis cannot be avoided[15,7~10].

The epoch is beginning to be made for controlling the superficial and deep-seated malignant tumors with the clinical application of interstitial hyperthermia, even though invasive, which it can safeguard the maximum normal tissue and cause to obtain a maximum therapeutic effects by reducing the treatment volume to a minimum as possible as it can[5~9,11].

There are two types of interstitial hyperthermia.

본 논문은 과학기술처 특정개발 과제연구비 보조로 이루어짐.

First, with interstitial applicators, microwave antennae or radiofrequency electrodes are surgically implanted into the tumor.

Second, with ferromagnetic seeds, thermoseeds are surgically implanted permanently into the tumor to create a deep uniform heating with a low-frequency magnetic induction field[5,7,9,10].

Several reports have suggested that the maximum therapeutic effect of hyperthermia could be obtained in combination with interstitial or external radiotherapy.

The purposes of our experiments were to obtain the experimental data about hyperthermia of cerebral cortex, to analyze the factors involved in the temperature distribution in vivo and to determine the appropriate control of temperature distribution by making dynamic and static phantoms and using them as human tissue alike.

Based upon these experimental data, we will try to apply the hyperthermia, especially interstitial, to in vivo tumors in the near future.

METHODS AND MATERIALS

1. Characteristics of Microwave Antenna

The microwave antenna, which we used, is single node type made for being operated with 915 MHz microwave. The junction is separated 3.5 cm from the end of antenna and the length of antenna is 35 cm. The distance to multi-channel distributor (MCD) is 120 cm and MCD is connected with 915 MHz generator through coaxial cable. 915 MHz generator has 4 channels, each of which can produce the maximum 100 watts respectively.

Power density of such an antenna in the air was measured with Narda Broadband Isotropic Radiation Monitor (Model 8611) and Model 8662 probe (Fig. 1).

2. Measurement of Temperature

When interstitial hyperthermia with microwave, was carried out thermal distribution in the treated volume was calibrated by using Sensortek clinical thermometer (Model TM-10A) and 3-inched Copper-constantan thermocouple general purpose probe (HF1) as a standard temperature.

We used 4 point Ga-As thermistor to maintain thermal stability, which was not impeded by thermosentry 1200 and 4 microwaves. We connected it with IBM PC and put in operation every day with the method of single point calibration at 43℃ and/or broad range calibration (19℃~56℃) and, thereafter, we used it in the experiment.

We regarded the failure level when deviation from standard temperature was more than 0.1℃ and warning level when more than 0.05℃.

Specific absorption rate (SAR) was calculated by using methods of Christensen and Roemer.

3. Phantoms

Dynamic phantom was designed and made for ourselves.

We made the Lucite box in which contained two vertically separated compartments. One compartment was regarded as phantom by using condensed sponge. Normal saline of 37℃ temperature ran through the lower part of one compartment into another compartment and draind out.

In order to protect the loss of heat by the atmospheric (room) air, we kept the air from permeating into the phantom by using Polyethylene of low linear density (Fig. 2).

4. Vital Tissues in Vivo

Malignant tumors originating from cerebral cortex are considered to be one of the most effective tumors when treated with intersititial hyperthermia.

As a basic study for confirming this fact, we tried to perform the interstitial hyperthermia with operative method and used cerebral cortices of cats with 2.5~3 kg body weights as materials (Fig. 3).

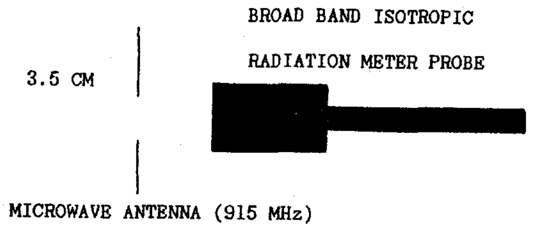

Fig. 1. Measurement method of power density produced by 915 MHz microwave interstitial antenna.

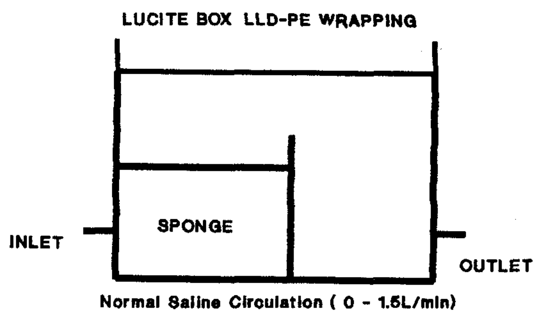

Fig. 2. Design of dynamic phantom for hyperthermia.

We have observed the behavioral changes of cats for at least 2 months after interstitial hyperthermia and pathologic findings in the cerebral cortices obtained from a small number of cats.

Prior to performance of the coming study about tumorous tissues in vivo, we observed the change of temperature when interrupted the blood circulation abruptly by injecting Entobar and concentrated KCl solution directly into the heart and we considered it as a model of tumorous tissues in vivo.

Various factors influencing on increase in temperature were turned out by performing interstitial hyperthermia quantitatively in the cerebral cortices isolated after autopsy.

RESULTS

1. Power Density in Air

Figure 4 represents that power density in air for 915 MHz microwave antenna with generation power of 1 watt showed western pear shape of 2 cm, 2 cm, and 6 cm in diameters when SAR 50% was considered as a standard (Fig 4).

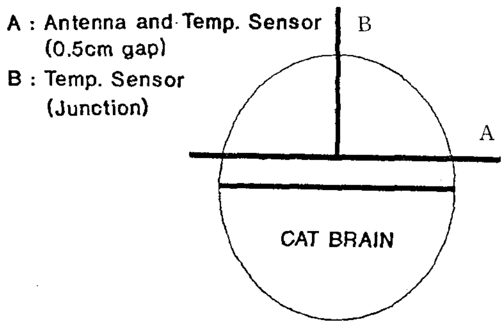

Fig. 3. Design of interstitial hyperthermia for cat brain.

2. Distribution of Temperature in the Static Phantom

The static phantom, in case that generating power of microwave antenna was 5 watts, showed that the shape of its temperature distribution was similar to that of power density in air when SAR 50% was considered as a standard.

As the time went by, however, continuous increase in temperature reached more higher than 55℃ of limiting temperature that could be measured with Ga-As thermistor (Fig. 5).

3. Distribution of Temperature in the Dynamic Phantom

While normal saline was flowing under the condition of 37℃ temperature, the distribution of temperature which was measured within the dynamic phantom, in case that generation power of microwave antenna was 5 watts, reached plateau within early 10 minutes, and this equilibrium state continued for more than 1 hour. When the flow of normal saline was stopped abruptly, the temperature continued to increase up to more higher than limiting temperature measured with Ga-As thermistor like in the static phantom (Fig. 6,7).

4. Safety on doing Interstitial Hyperthermia of Cerebral Cortices of Cats

We performed craniectomies in cats with body

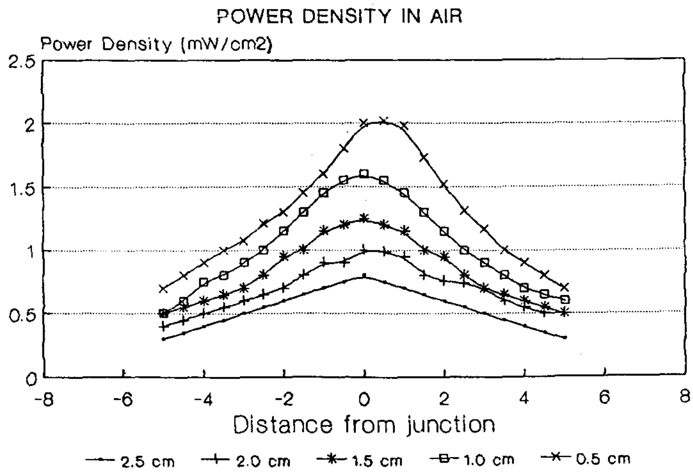

Fig. 4. Power densities in air for 915 MHz microwave interstitial antenna.

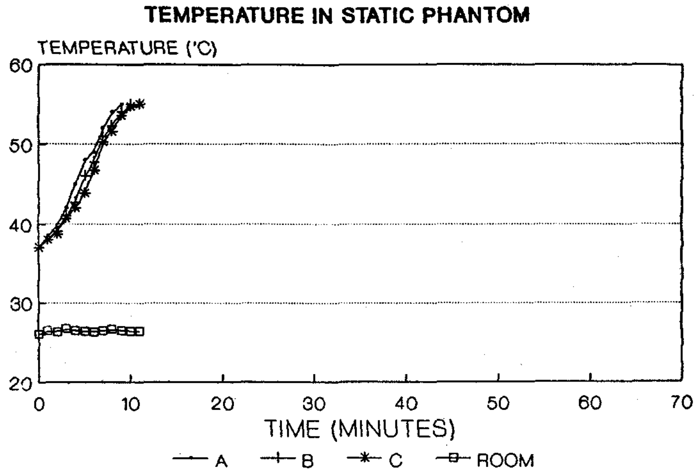

Fig. 5. Temperatures changes in static phantom during 915 MHz microwave interstitial hyperthermia.

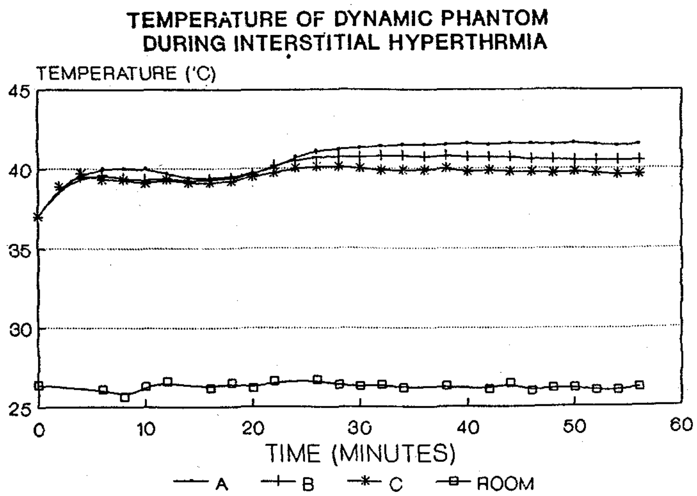

Fig. 6. Temperatures changes in dynamic phantom during 915 MHz microwave interstitial hypethermia.

weights of 2.5~3.0 kg. One cat was dead during operation and so interstitial hyperthermia could not be carried out. The cause of death might be probably an active bleeding. Another cat developed ipsilateral hemiparesis on the following day after interstitial hyperthermia and it was, we thought, due to intracranial hematoma having occurred during operation.

5. Distribution of Temperature on doing Interstitial Hyperthermia of Cat Brain

At the start of our experiment, we used HCl -Ketamine as an anesthetic which was injected into the muscle, resulting in stage III narcosis. Recently we maintained the narcotic state of cats with Entobar [2,4,6, (1H,3H,5H)-pyrimidinetrione-5-ethyl-5 (1-methylbutyl) monosodium salt] injected into the peritoneal cavity.

After cat was fixed with fixation device invented by neurosurgical department of our hospital, right frontoparietal craniectomy was carried out. Sixteen gauged blind-ended catheter was penetrated through the exposed right cerebral hemisphere in order that the junctional area of microwave antenna

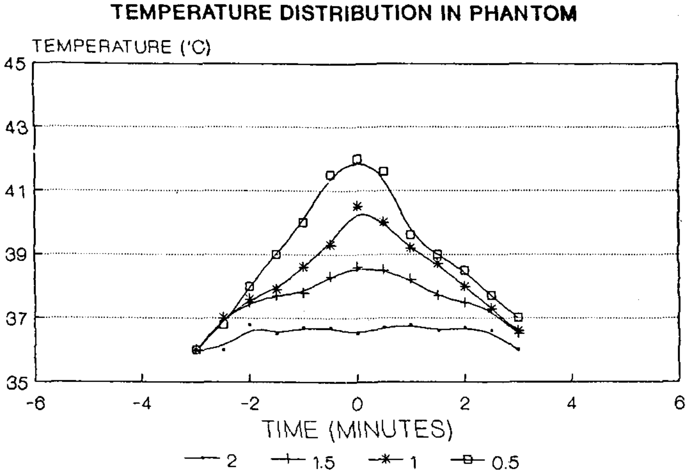

Fig. 7. Temperature distribution in dynamic phantom during 915 MHz microwave interstitial hyperthermia.

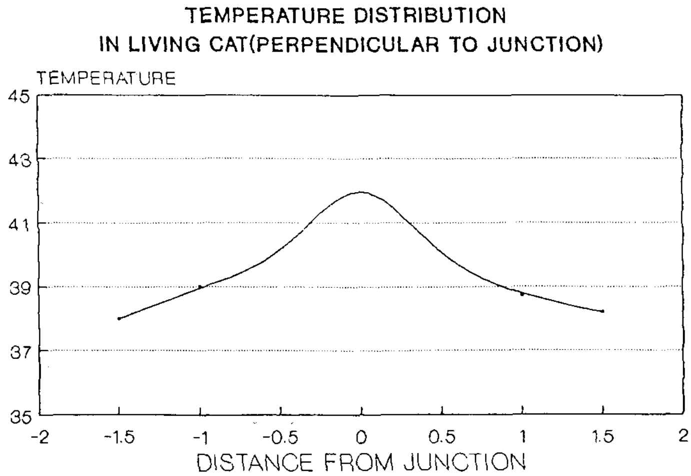

Fig. 8. Temperatures changes in living cat brain during 915 MHz microwave interstitial hyperthermia.

might be located in the center of right cerebral hemisphere.

Parallel to this catheter, another with 16 gauge blind-ended catheter was inserted 0.5 cm superiorly and the other inserted perpendicularly to them. The precise location of these catheters was verified with simulator in our department.

Thereafter, we carried out intersitial hyperthermia and measured the distribution of temperature, resulting in the equilibrium or steady state of 43℃, maximum temperature, with generating power of 5 watts.

This steady state maintained for 45 minutes, and its distribution involved the entirety of ipsilateral cerebral parenchyme as treated volume in cases of 50% SAR (Fig. 8~10).

6. Change of Temperature on doing Interstitial Hyperthermia of Cat's Cerebral Cortices Before and After Interruption of Circulation

On doing interstitial hyperthermia of cat's cerebral cortex, Entobar and concentrated KCl solution were injected into heart to interrupt blood circulation in a moment. The temperature in the cerebral cortex, measured with Ga-As fiberoptic thermistor, was found to be more higher than limiting tempera-

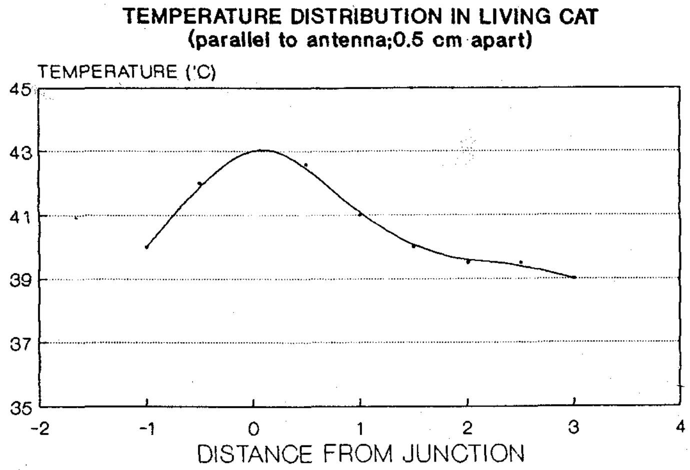

Fig. 9. Temperature distributions in cat brain perpendicular to antenna junction during 915 MHz microwave interstitial hyperthermia.

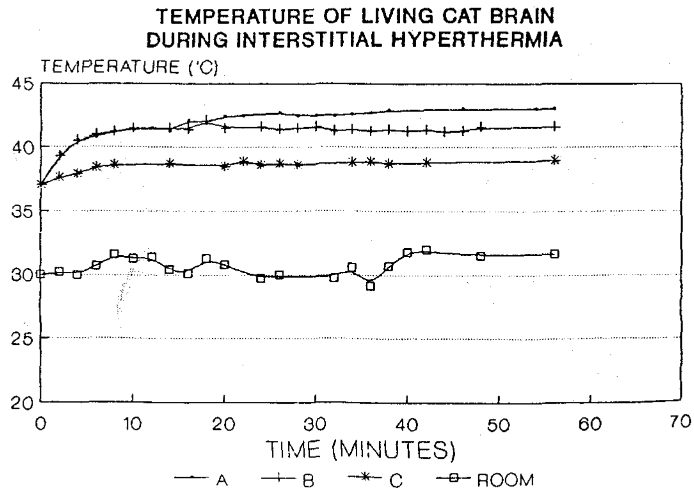

Fig. 10. Temperature distributions in cat brain along antenna during 915 MHz microwave interstitial hyperthermia.

ture of 55℃ within 5 minutes (Fig. 11).

After cats were decapitated with the catheters in their original positions, microwave antennae applied heat to three catheters with generating powers of 5,10 and 15 watts respectiely. The results of heating were that temperatures reached the limitimg temperature of 55℃ in 15.2 minutes (SE . 4), 9.7 minutes (SE .3), and 6.3 minutes (SE .4) respectively (Fig. 12).

DISCUSSION

Many efforts have incessantly been made to improve the treatment results of malignant brain tumors known to be incurable by only external irradiation.

Owing to the development of diagnostic tools such as CT and MRI, we could know the precise locations about malignant brain tumors and so many a method has been studied to irradiate more radiation dose to the tumors than the surrounding normal tissues.

Recently we started to perform a stereotactic brain implantation with Ir-192. On the basis of this technique, we decided to perform a interstitial hyperthermia only or combined with interstitial Ir-

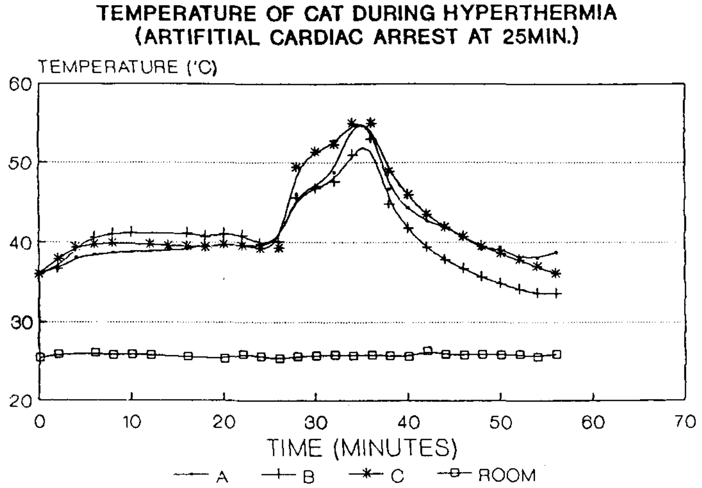

Fig. 11. Temperature change in cat brain during 915 MHz microwave interstitial hyperthermia (sacrified after 25 minutes of static period of hypethermia).

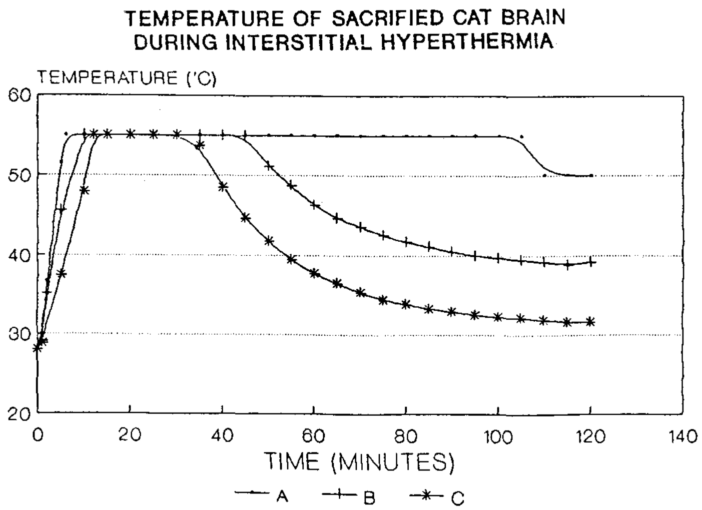

Fig. 12. Temperature changes in sacrified cat brain during 915 MHz microwave hyperthermia with various power (5,10,15 Watts).

192 implantation[14].

To do this, it is necessary for us to know the precise distribution of temperature within both tumors and surrounding normal brain tissues and subsequent complications due to thermal injury.

First of all, we made a dynamic phantom similar to human beings' tissues for ourselves and performed interstitial hyperthermia. On the basis of it, we performed interstitial hyperthermia in living cat brain to elucidate the temperature distribution and the effect of circulation on the temperature.

In case of no circulation (in static phantom), as heat was applied, temperature rose continously up to the level not measured with Ga-As thermistor. In dynamic phantom with circultation of normal saline as a substitute for blood, temperature reached the equilibrium state or plateau phase within early 10 minutes and there was no further rising in temperature.

To the contrary, when we interrupted the circulation, temperature rose up to more higher than the limiting temperature, 55℃, not measured with

Ga-As thermistor as well as in static phantom.

Next, we observed that the temperature reached maximum of 43℃ with generating power of 5 watts when performed in living cat brain. But when we interrupted the blood cirulation by injecting Entobar and concentrated KCl solution into the heart in a moment, the temperature rose rapidly up to more higher than 55℃ within 5 minutes.

After decapitation, we measured the lapse of time within which temperature reached the limiting one, 55℃, under variable generation powers (5,10 and 15 watts). The result was that the higher generating powers, the shorter time elapsed to reach the limiting temperature.

Therefore, we could conclude that circulation might play an important role in reducing thermal damage by dissipating heat over limiting temperature of normal tissue tolerance and so decreasing complication rate subsequent to interstitial hyperthermia.

In the near future we will repeat the abovementioned experiment in the state of the presence of tumor transplantable experimentally, and find out the mechanism which may control the distribution of temperature and increase the blood flow or vascular volume on the cellular level[15].

REFERENCES

1. **박찬일, 고경환, 하성환** : 초음파를 이용한 온열치료시 온도분포에 관한 연구. 대한치료방사선과학회지 2(1):21-23, 1984
2. **고경환**: 항암 온열치료 (I) 생물학적 기본원리. 진단과 치료 7:307-312, 1987
3. **고경환**: 항암 온열치료 (II) 기구 및 방법. 진단과 치료 7:431-433, 1987
4. **고경환**: 항암 온열치료 (III) 임상진단과 치료. 7:554-558, 1987
5. **KH Koh, YH Park, CK Cho, SY Yoo**: Clinical applications of microwave and ultrasound in hyperthermia: Preliminary results. J Korean Soc Ther Radiol 6(1):75-80, 1988
6. **Hahn GM**: Hyperthermia and cancer. New York, Plenum Press 1982
7. **Oleson JR, Deshirst MW**: Hyperthermia; An overview of current progress and problems. CP Ca 83(12):1-62, 1983
8. **Marmor JB, Pounds D, Postic TB, et al**: Treatment of superficial human neoplasm by local hyperthermia induced by ultrasound. Cancer 43:188-197, 1979
9. **Perez CA, Emami B**: A review of current clinical experience with Irradiation and hyperthermia. Endocurietherapy/Hyperthermia Oncol 1(4):265-277, 1985
10. **Noell KT, Woodward KF, Worde BT, et al**: Microwave induced local hyperthermia in combination with radiotherapy of human malignant tumors. Cancer 45:638-646, 1980
11. **Hand JW, Ter Harr G**: Heating techniques in hyperthermia, I, II, III. Br J Radiol 54:443-466, 1981
12. **Christensen D**: Thermal dosimetry and temperature measurement. Cancer Res 39:2325-2327, 1987
13. **Roemer RB, Cetas TC**: Applications of bioheat transfer stimulations in hyperthermia. Cancer Res (Suppl) 44(10):4788s-4798s, 1984
14. **Cosset JM, Dutreix J, Hale C, et al**: Interstitial thermoradiotherapy: a technical and clinical study of 29 implantations performed at the Institut Gustave-Roussy. Int J Hyperthermia Vol 1, No 1,3-13, 1985
15. **Reinhold HS, Endrich B**: Tumor microcirculation as a target for hyperthermia. Int J Hyperthermia Vol 2, No 2, 111-137, 1986

국문초록 =

915 MHz 극초단파 자입온열시 온도분포 적정화에 관한 연구

—조직등가물 및 가묘대뇌를 대상으로—

원자력병원 치료방사선과 · 신경외과*

고경환 · 조철구 · 박영환 · 류성렬 · 김종현* · 이승훈*

원자력병원 치료방사선과에서는 자입온열치료 등을 위한 역동적 조직 등가물을 자체 고안하여 제작된 역동적 조직등가물에서 얻은 결과와 실제 가묘 대뇌실질에 자입온열치료를 시행해서 얻은 결과에서 다음과 같은 결론에 도달하여 향후 인위적으로 유발시킨 가묘 대뇌실질 내 악성종양에 대한 실험적 연구의 기초가 되고 암치료율 향상을 위한 시발로 삼으려 한다.

1. 915 MHz 극초단파를 이용한 자입온열기 단말의 치료가능 용적은 50% S.A.R. (specific absorption rate)에 의하면 2 cm×2 cm×6 cm이었다.

2. 순환이 되지 않는 정적 조직등가물에서는 공기 중 압력분포와 같았고 자입온열치료기 가동후 5~10분 내에 극초단파에 의해 간섭받지 않는 Ga-As fiberoptic thermistor로 측정되지 않는 55℃ 이상의 온도 이상으로 상승됨이 관찰되었다.

3. 생리식염수를 순환시킨 역동적 조직등가물에서 자입온열치료기 가동 후 5분 이내의 경과기 (transit period)를 거쳐 45분 이상의 안정기 (steady peroid)를 얻을 수 있었다.

4. 역동적 조직등가물에서 순환을 차단하면 정적 등가물과 같은 온도 상승이 관찰되었다.

5. 가묘 대뇌실질에 대한 자입온열치료를 5 Watts 이하의 출력으로 사용하는 경우 비교적 안정되게 시행 가능했고 순환차단에 의한 급격한 온도상승이 관찰되었고 최고 55℃ 이상까지 걸리는 시간이 출력 5, 10 및 15 Watts에서 각각 15.2 (SE 0.4), 9.7 (SE 0.3) 그리고 6.3 (SE 0.4)분 이었다.

본 연구는 기초 생물학적 실험이지만, 그 결과는 임상 암치료 방법에 직접 이용되는 것이며 또한 치료수행을 위해 반드시 필요한 과정이다. 따라서 치료방법의 결정, 성적분석, 치료 부작용의 예측 및 대책확립 등에 적용될 뿐만 아니라, 외국의 치료결과와 비교시 본원 온열치료의 특성제시에 활용될 수 있다.