기관고유연구사업 결과보고서

(과제번호 : 0610650)

뇌암에 대한 수술중 고열치료법 (전임상실험)

Intraoperative hyperthermia in the treatment of malignant brain tumor (preclinical study)

과제책임자 : 유 헌

국 립 암 센 터

제 출 문

국립암센터 원장 귀하

이 보고서를 기관고유연구사업 “ **뇌암에 대한 수술중 고열치료법 (전임상실험)**” 과제의 결과보고서로 제출합니다.

2007. 1 . 25

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목 차

< 요 약 문 >

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<table>
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<tr><td>영문</td><td colspan="5">intraoperative hyperthermia, malignant brain tumor</td></tr>
</table>

◆ 연구목표

<최종목표>

-뇌암에 대한 고열치료법을 위해 독창적인 고열종양치료기를 개발하고 그 장치의 생체역학적 특성과 안정성을 평가함.

<당해연도목표>

1차년도

-고열종양치료기의 생체역학적 특성 측정

-시제품의 개량

2차년도

-수술 중 고열종양치료기의 생체내 작용 특성 및 안정성 평가

◆ 연구내용 및 방법

-고열종양치료기의 생체역학적 특성 측정

1) 순환하는 수온에 따른 뇌 조직내 온도 분포도 작성

2) 뇌조직의 병리학적 변화

-수술 중 고열종양치료기의 생체내 작용 특성 및 안정성 평가

1) 1차년도에 축척된 data를 바탕으로 고열종양치료기를 개량하고 기구의 조건 및 크기를 다양하게 변화시키고 DITI(Digital Infrared Thermal Imaging)를 접목시켜 실시간으로 열분포를 감시할 수 있도록 발전시키도록 함.

2) 시술후 장기간 사육하면서 안정성 평가

conventional pig 3마리(한 마리:1주일, 두 마리: 1개월) 사육 및 MRI촬영, 병리분석

SPF pig 6마리 (6개월) 사육 및 MRI 촬영, 병리분석

-시제품의 개량

1) 고열종양치료기 고정 장치를 개발

2) 치료기구(Hyperthermic probe: 이하 probe로 표기함)의 개선

기존의 16mm, 20mm이외에도 13mm,18mm,21mm,25mm,30mm,35mm,40mm, 45mm의 probe를 제작하여 동물실험 및 임상실험을 위한 적용점을 넓힘.

3) water bath의 개선

현재의 system에서 sterile procedure가 가능하도록 system의 개선을 시행.

4) 온도제어 시스템의 개선을 통하여 치료온도의 정밀제어를 가능하게 함.

5) digital thermal flowmeter를 개발하여 온도계측의 직관화, 저장 및 feedback system개발

◆ 연구성과

-정량적 성과

구분	달성치/목표치[1)]	달성도(%)
SCI 논문 편수		
IF 합		
기타 성과	발명특허(국내 10-2006-0042451) 발명특허출원(미국11-789059,유럽 07-008688.9,일본 2007-124448)	

1) 총연구기간내 목표 연구성과로 기 제출한 값

-정성적 성과

고열종양치료기의 생체 내 작용 특성에 관한 기본 data 구축

DITI를 접목하여 치료범위 확인 및 data구축

실험동물의 장기사육 및 MRI, 신경행동분석, 병리검사를 통하여 안정성확보

고열종양치료기의 다양한 크기의 probe 개발

Digital flowmeter를 개발하여 접목시킴

임상시험을 위한 closed sterile system을 개발

◆ 참여연구원 (최종연도 참여인원)	성 명	유 헌, 조영호, 신상훈, 이승훈, 양희석
	주민등록번호	

Project Summary

Title of Project	Intraoperative hyperthermia in the treatment of malignant brain tumor (preclinical study)
Key Words	intraoperative hyperthermia, malignant brain tumor
Project Leader	Heon Yoo
Associated Company	

We have invented a new hyperthermic system that is consisted of water heater and pump, sphere probe, temperature sensor and display, water inlet and outlet tube. Using this system,the adjuvant treatment could be done to surgical bed that tumors were removed gross totally or left because of difficult surgical access or functional reasons.

A total of 5 male conventional pigs and 6 SPF pigs were used for animal study. A cortisectomy with the depth of 14 mm was done to the right frontal lobe and the hyperthermic probes were placed into the cortisectomy cavity with temperature and time protocol. Two pigs (Pig 1 and 2) were sacrificed on the day of treatment to obtain acute histologic analyses. Three pigs (Pig 3,4 and 5) were allowed to survive for various time period (pig 3 for 7 days, pig 4 and 5 for 30 days)to to allow us to study time-related changes in the results of histological analyses. Six pigs (Pig 6-11) have been bred for long-term safety study. After thermal treatment, they were observed with daily neurological exam by veterinary.

We have applied DITI during hyperthermia treatment and compared thermal data between DITI and thermometry catheter. DITI was applied to 3 pigs(pig 3-5) during hyperthermia treatment. Thermal data from thermometry catheter and calculated from DITI system was collected and compared. MRI was performed with a 1.5 T whole-body MR scanner. For gross pathologic evaluation, brains were excised and all slides wre interpreted by a pathologist with experience in neuropathology. The changes in the appearance of thermal lesions on MR images were compared with results of histologic analyses. Behavior and neurologic examinations included foreleg position, struggles when caught, albe to lift head up, whole body sway when walk, gait analyses and cranial nerve function. The results of behavior and neurologic study was normal for all pigs during study.

We described the effects of hyperthermia with a newly designed hyperthermic system with sphere probe. We have evaluated the characteristics of newly developed hyperthermic system for clinical trial. This hyperthermic system with sphere probe is a suitable technique for the treatment of brain tumors after surgical removal to control the recurrence. However, a definite mechanisms of hyperthermia and actual result of clinical trial should be shown with further stydy.

1. 연구사업의 최종목표

From ancient times to the present, man has dreamed of utilizing elevated temperatures(hyperthermia) in the treatment of malignant tumors. This desire has been consistently frustrated by technological limitations on our ability to deliver heat deep within the body in such a way that normal surrounding tissues remain unharmed. we have invented and developed new hyperthermic treatment system for brain tumors and evaluated biophysical profiles and short-term and long term safety.

2. 연구사업의 내용 및 결과

Development and improvement of a new hyperthermia system

We have invented a new hyperthermic system that is consisted of water heater and pump, sphere probe, temperature sensor and display, water inlet and outlet tube. Using this system,the adjuvant treatment could be done to surgical bed that tumors were removed gross totally or left because of difficult surgical access or functional reasons.(Fig. 1.)

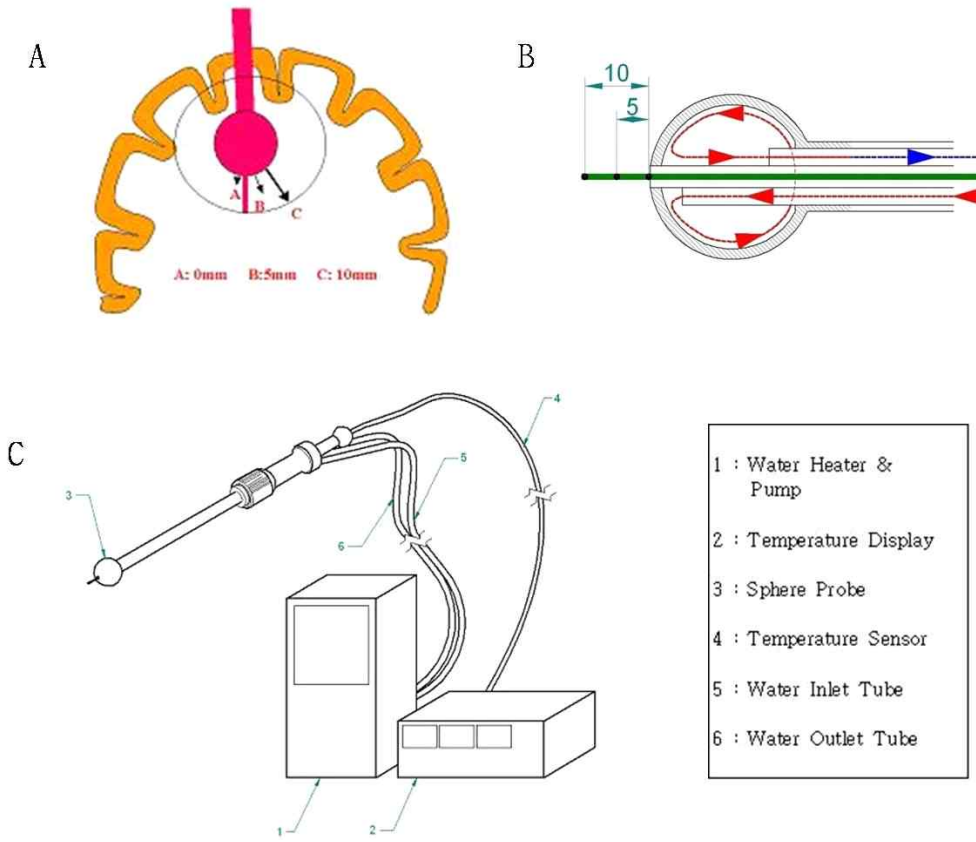


Fig.1. The schematic drawing of hyperthermic system for brain tumors after surgical removal. A.With heating probe, the target areas are ranged within 1cm from sphere. B.The sphere probe have water inlet and water outlet tube. The heated water flows within spere and

the water flow and temperature are controlled by thermal monitoring and regulation system. C. The drawing of 6 parts consisting hyperthermic system.

Deveopment of hyperthermic system for clinical use

The water heater and pump system must generate enough heat to raise the temperature around tumor bed and control the temperature precisely. Therefore, important factors related to water heater system and temperature control system were revised several times. We has designed and developed, the new hyperthermic equipment and this system is highly efficient for hyperthermia to large volume. The specifications of our system are as follows: the sphere probe, diameter from 10mm to 45mm; temperature sensors and display, which record profiles and control general operation of heating system; water heater and pump system, which are controlled by thermal data and supply precise thermal energy to probes and target lesions. For clinical apply, closed sterile system is developed using closed heating system (Fig.2. and Fig.3.) The material of spere probe is histocompatible. The safety and stability of this material for clinical use have been confirmed by chemical and biological test.

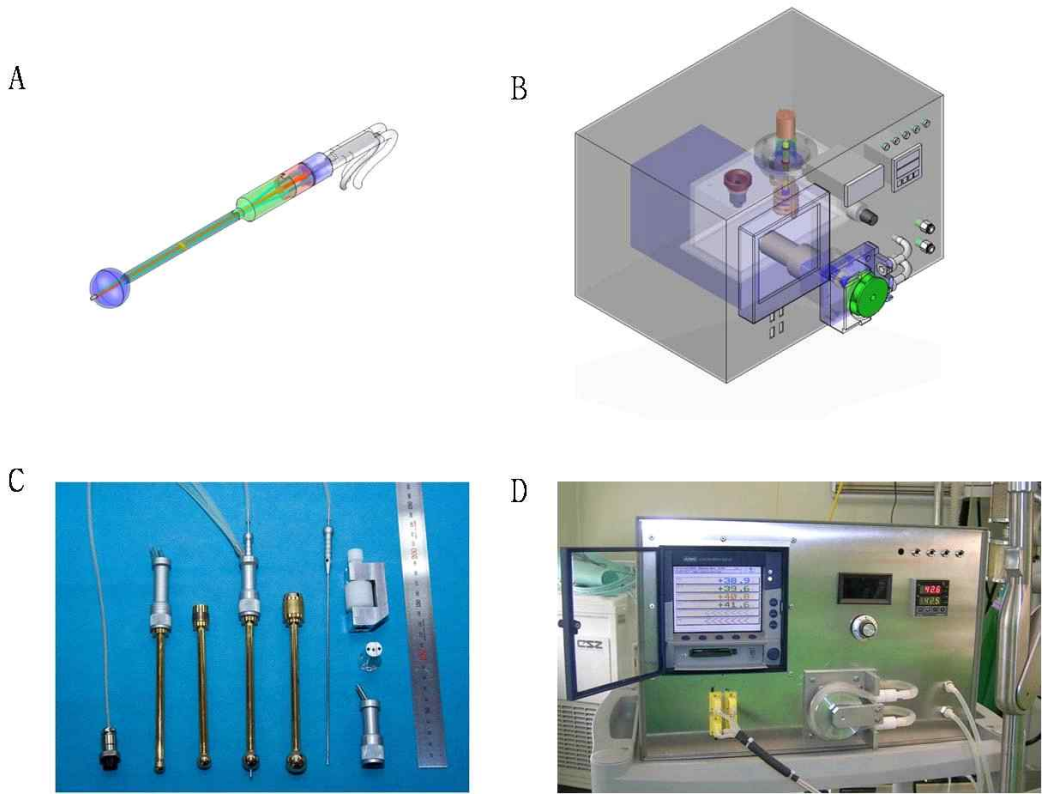


Fig. 2. Development of hyperthermic system for clinical use.

A and B. Skematic 3D drawing of thermal probe, water heater and pump system. C and D.

Photographs of hyperthermic system.

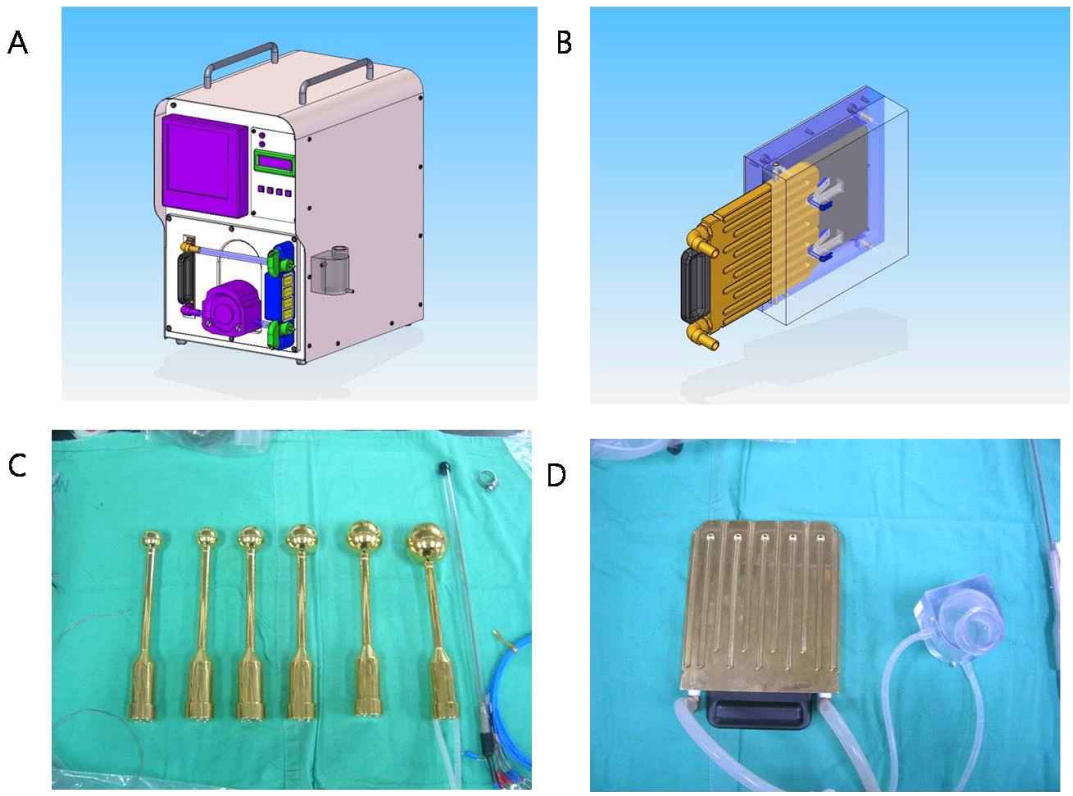


Fig. 3. Development of closed sterile hyperthermic system .

A and B. Skematic 3D drawing of closed circit and heating system. C and D. Photographs of newly deveoped probes(25-45mm) and heating pannel.

In Vivo study of a New Hyperthermic system and Safety study

Animals

A total of 5 male conventional pigs (40kg) and 6 SPF pigs(3 male and 3 female) were obtained from PWG genetics Korea, Ltd(Pyeongtaek,Korea).

Anesthesia for surgical procedures and imaging was induced with intramuscular meditomidine (10mg/kg) and maintained with 2% isoflurane.

The pigs were placed in the prone position. A midline skin incision was made on the vertex of the skull, and a craniectomy was made with high speed drill. A wide dural opening exposed right hemisphere. A cortisectomy with the depth of 14 mm was done to the right frontal lobe with bipolar and suction. The hyperthermic probes were placed into the cortisectomy cavity with variable temperature and time protocol. During thermal application, the temperature changes at the brain and body were recorded continously. After completion of

each study protochol, the pigs were killed with a KCL injection, and the brains were removed and examined microscopically.

To minimize reactive brain edema after thermal treatment, prednisone treatments were used. Prednisone was administered orally twice daily at a dose of 2mg/kg on the day of treatment and at decreasing dose on each of next 6 days.

Two pigs (Pig 1 and 2) were sacrificed on the day of treatment to obtain acute histologic analyses. Three pigs (Pig 3,4 and 5) were allowed to survive for various time period (pig 3 for 7 days, pig 4 and 5 for 30 days)to to allow us to study time-related changes in the results of histological analyses. Six pigs (Pig 6-11) have been bred for long-term safety study. After thermal treatment, they were observed with daily neurological exam by veterinary.

Basic data of thermal distribution experiments in the pigs

The basic thermal distibution experiments were performed on two pigs(Pig 1,2). The hyperthermic probes were placed in the cavities and hyperthrmic treatments were applied with variable temperatures. The temperature changes at 0mm,5mm and 10mm depth aroud probe were recorded continously with the thermometer. The histologic analyses were done after hyperthermic treatments.

A correlation between tissue temperatures and distance from the hyperthermic probes was noted. The temperature 5mm away was 42.5°C after 3 minutes at 54°C water-bath, at 0mm it was 51°C and at 10mm it was 38.8°C, and the body temperature was 38.8°C. Each temperature remained constant after 3 minutes at each water-bath temperature. Thermal dosimetry plot from thermometry catheter in the frontal white matter of the pig brain as a function of time and temperature of water-bath is shown in Fig. 4.

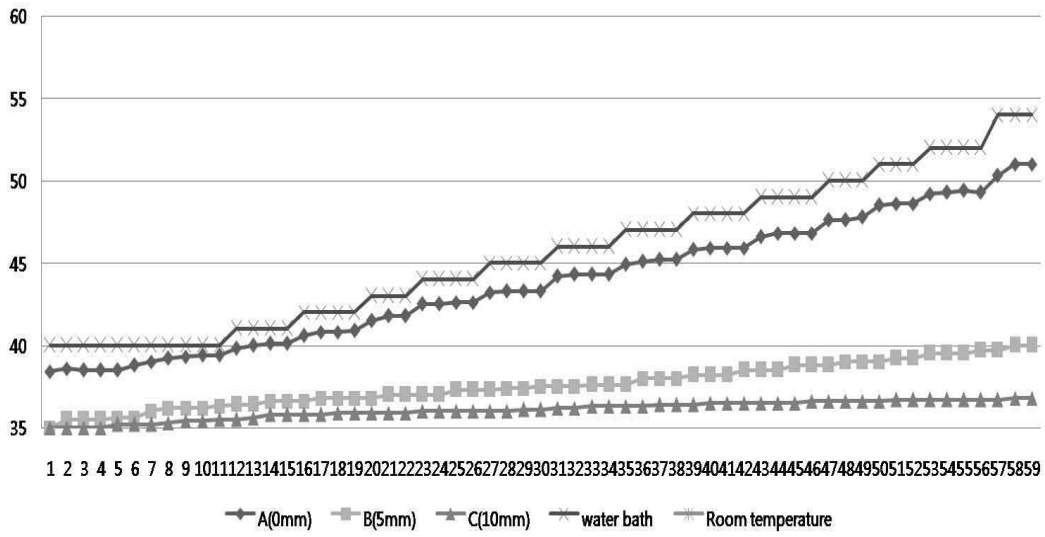


Fig. 4. Thermal distribution of hyperthermia treatment in pig.

Thermal dosimetry plot from thermo-probe in the frontal white matter of the pig brain as a function of time and temperature of water-bath. The temperature 5mm distant from thermal

probe was 42.5°C, the temperature 0mm distance, 10mm distance were 51°C and 38°C each and the body temperature was 38°C at 54°C with water bath.

The application of Digital Infrared Thermal Imaging(DITI)

Hyperthermia was monitored with implanted thermometry catheter. But the thermometry catheter collects the thermal data only around the catherer inserted. We have applied DITI during hyperthermia treatment and compared thermal data between DITI and thermometry catheter. DITI camera was commercially available(NEC, Japan).

DITI was applied to 3 pigs(pig 3-5) during hyperthermia treatment. Thermal data from thermometry catheter and calculated from DITI system was collected and compared.(Fig.5.)

With DITI, it colud not monitor thermal profile deep-seated area. But with 2-dimensional thermal profile, there were the correspondence of DITI results with thermometry catheter.

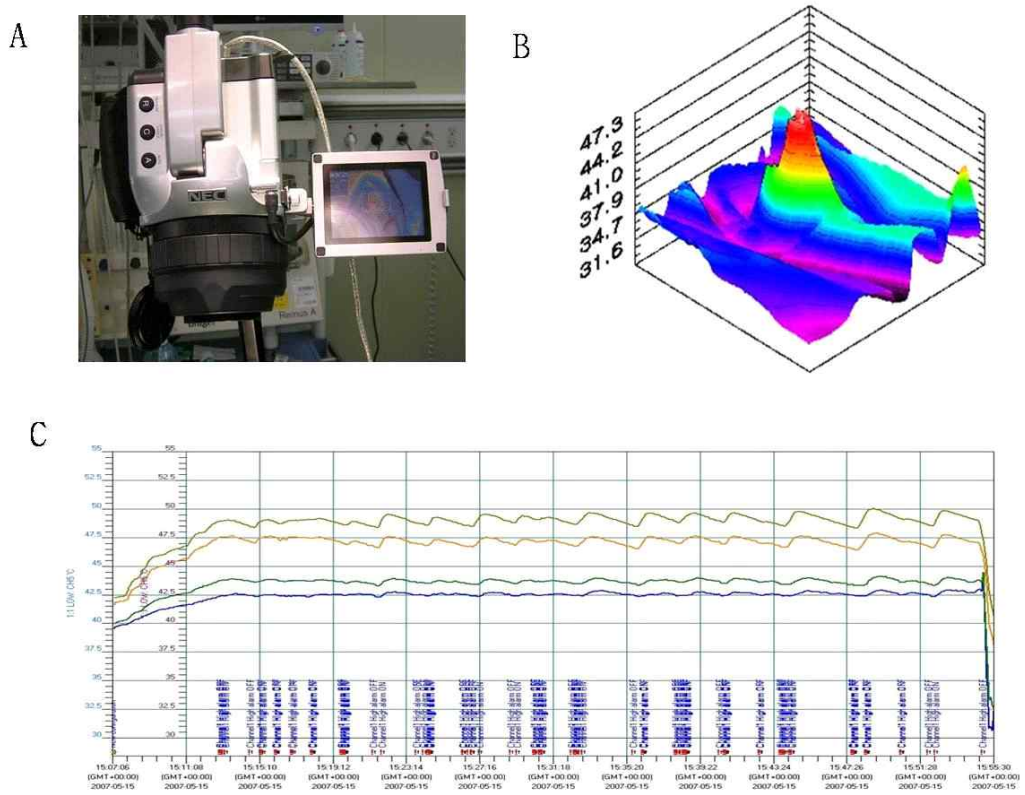


Fig. 5. The application of Digital Infrared Thermal Imaging to hyperthermia. A. Digital Infrared Thermal Imaging camera, commercially available (NEC, Japan). B. Thermal data from DITI system. C. Thermal profile from thermometry cahtheter.

MRI

MRI was performed with a 1.5 T whole-body MR scanner(GE Medical System, Sigma

Echospeed, Milwaukee, WI). The anesthetized pigs were positioned headfirst and supine in the scanner, using a standard MR couch with a frame designed to minimize motion.

Coronal MR images were serially acquired in spine-echo T1 weighted images, fast spin-echo T2-weighted images and T1-weighted gadolium-enhanced images. For contrast-enhanced studies, an intravenous injection of 0.2 ml/kg of gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) was administrated prior acquiring T1-weighted images.

The settings for the spin-echo T1-weighted images were as follows: TR, 350 milliseconds; TE, 9 milliseconds; BW, 16 kHz; phase x freqeuncy matrix, 160 x 256; FOV, 14 x 14 cm; section thickness, 2mm; and intersection gap, 1mm. The settings for the fast spin-echo T2 weighted images were: TR, 3000 milliseconds;TE, 102 milliseconds; echo train length, 12;phase x frequecy matrix, 192 x 256; FOV, 14x 14 cm; section thickness, 2mm; and intersection gap, 1mm.

Gross and Histopathologic Analyses

For gross pathologic evaluation, brains were excised and fixed by immersion in a 10% phosphate buffered formalin solution for 7 days. The brain were then cut coronally into slices that were approximately 3mm thick and approximately parallel to the direction of the coronal MR slice that was used. The formalin-fixed slices underwent standard histologi processing, and section 4-6 m thick were cut and stained with hematoxylin-erosin stain. All slides wre interpreted by a pathologist with experience in neuropathology. Digital photographs of each tissue slide and the resulting stained section were taken using high-resolution digital camera.

Short-term and long-term analyses of hyperthermic treatment with 42.5°C at 5mm depth

The hyperthermic probes were placed in the cortisectomy cavities and hyperthermic treatment were done with 42.5°C at the 5mm depth in the brain for both 40 minutes and 60 minutes. Two pigs(pig 4 and 5) were bred for one months, one pig(Pig 3) for 7 days, and 6 pigs(pig 6-11) have been bred in the schedule of 6 month breeding. MR images were performed at one month after hyperthermic treatment(pig 4-11) and have been scheduled at 3 month and 6 month after treatment(pig 6-11). The behaviour analyses including neurological exams were performed by veterinary. After completion of each protocol, the brains were removed and examined by pathologist. The changes in the appearance of thermal lesions on MR images were compared with results of histologic analyses.

Short-term follow-up MRI at 1 month after hyperthermia is shown in Fig.6. The histological analyses was done after MRI evaluation at 1 month with short-term follow group and is shown in Fig.7. Behavior and neurologic examinations included foreleg position, struggles when caught, albe to lift head up, whole body sway when walk, gait analyses and cranial nerve function. The results of behavior and neurologic study was normal for 6 pigs during study. With long-term follow-up group, they have taken 1 month follow-up MRI after hyperthermia treatment(Fig.4.5.) and have scheduled to have 6 month follow-up MRI. They have been under close observation by veterianary with the view of behavior analysis. After completion of each

protocol, the brains were removed and examined by pathologist. The changes in the appearance of thermal lesions on MR images were compared with results of histologic analyses.

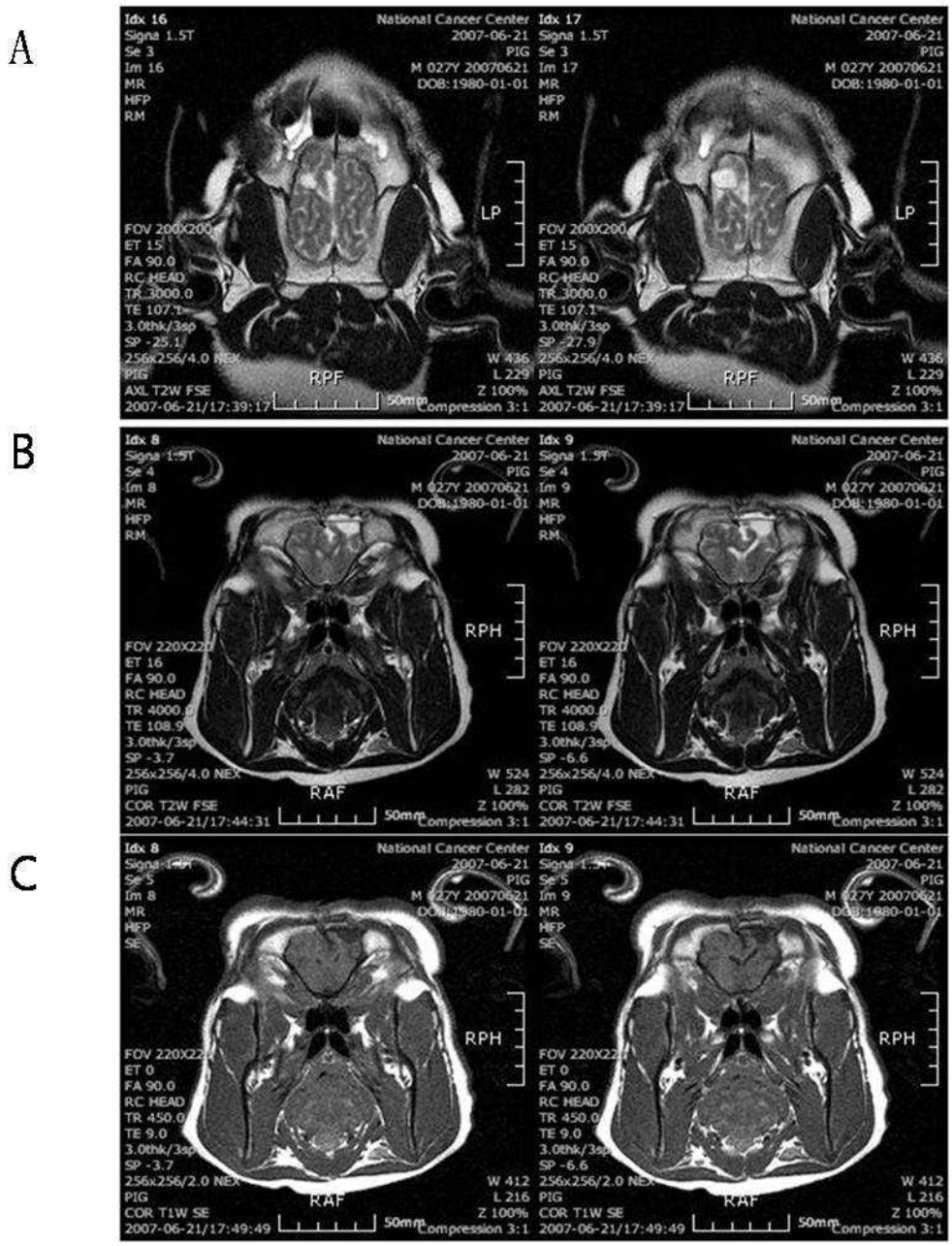


Fig. 6. MRI at 1 month after hyperthermia (Pig 5)

MR images obtained at 1 month after hyperthermic treatment. A.Axial T2-weighted MR images. B. Coronal T2-weighted MR images.C. Coronal T1-weighted gadolinium-enhanced MR images.

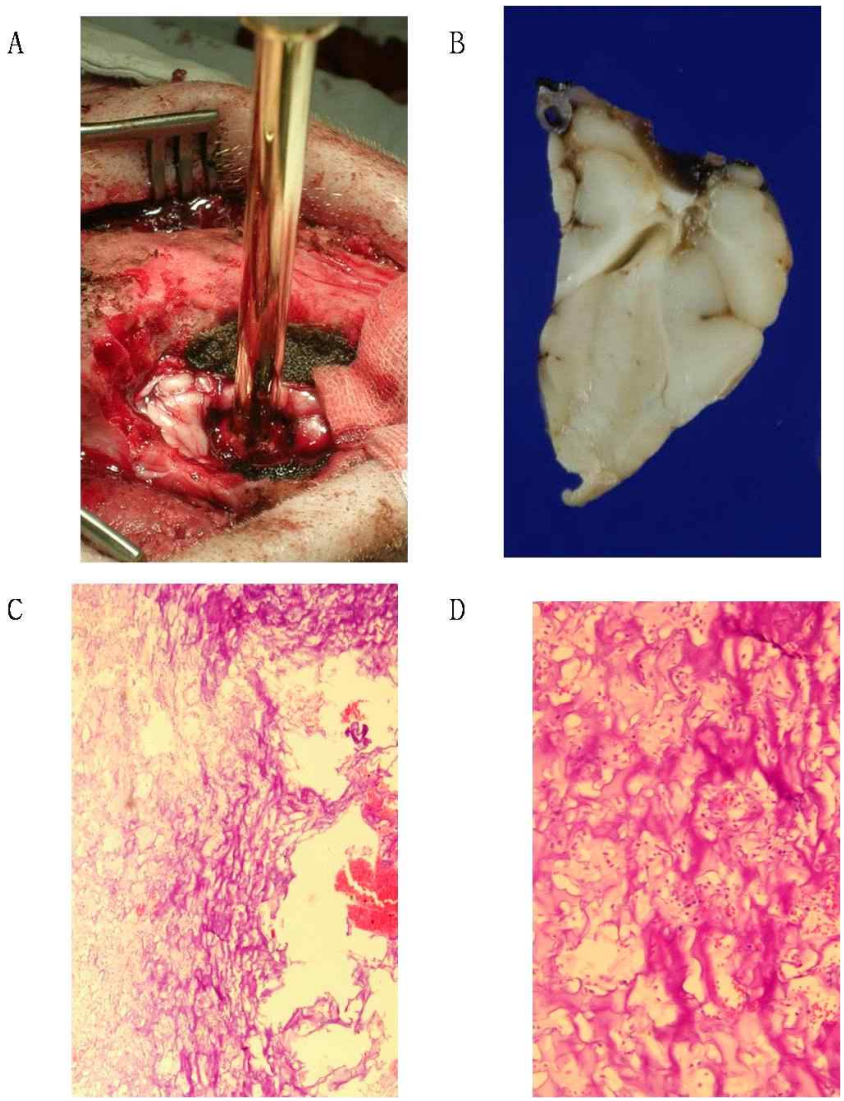
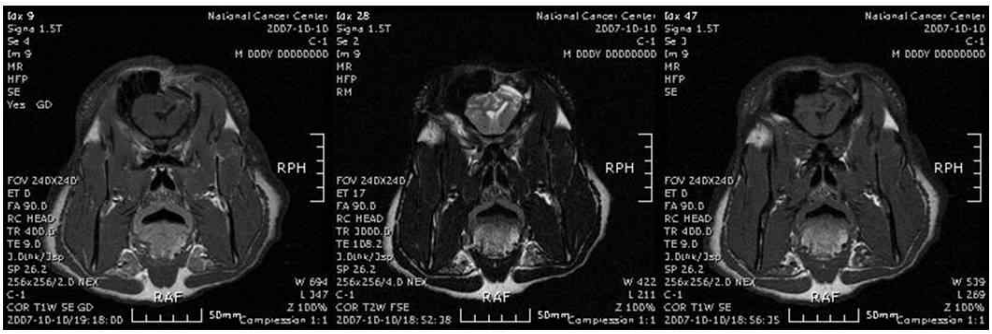


Fig 7. Histologic analyses at 1 month after hyperthermia.

A. Photograph of hyperthermia treatment with sphere probe in pig brain. B. photograph showing the pig brain section, partial destruction of pig brain by moderate hyperthermia at 42.5°C for 60 minutes. Complete destruction extend to 2 mm depth from the bed after hyperthermia treatment. C. Photograph showing partial pyknosis and cytoplasmic degeneration on the right side, surrounded by foam cells and inflammatory cells including lymphocytes or neutrophils. The adjacent brain parenchyme shows reactive gliosis. HE staining, X 40.D. Photograph with x 100 of C.

A



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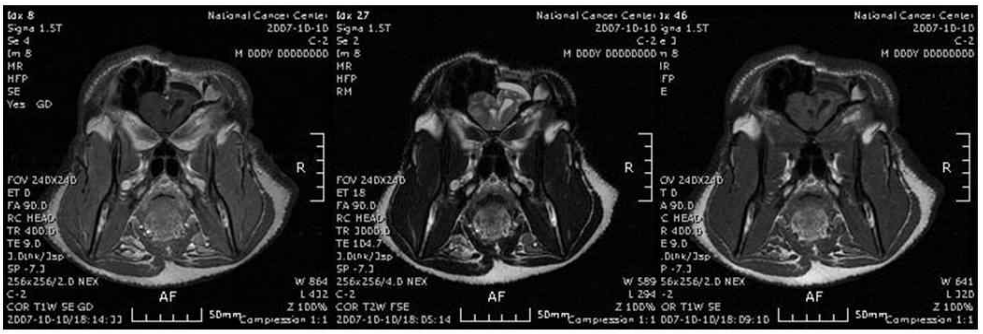

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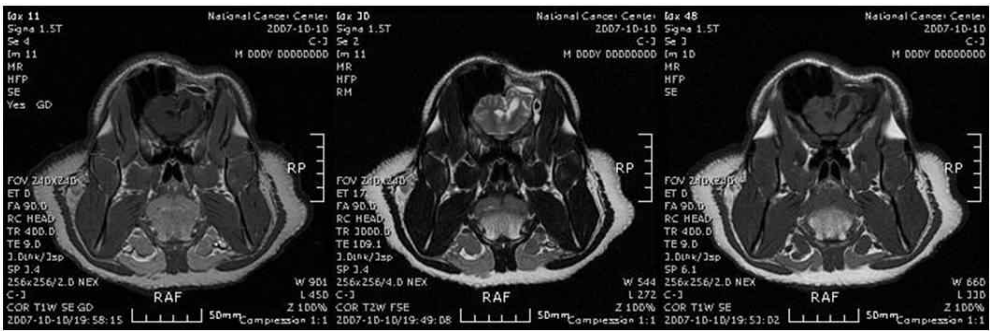

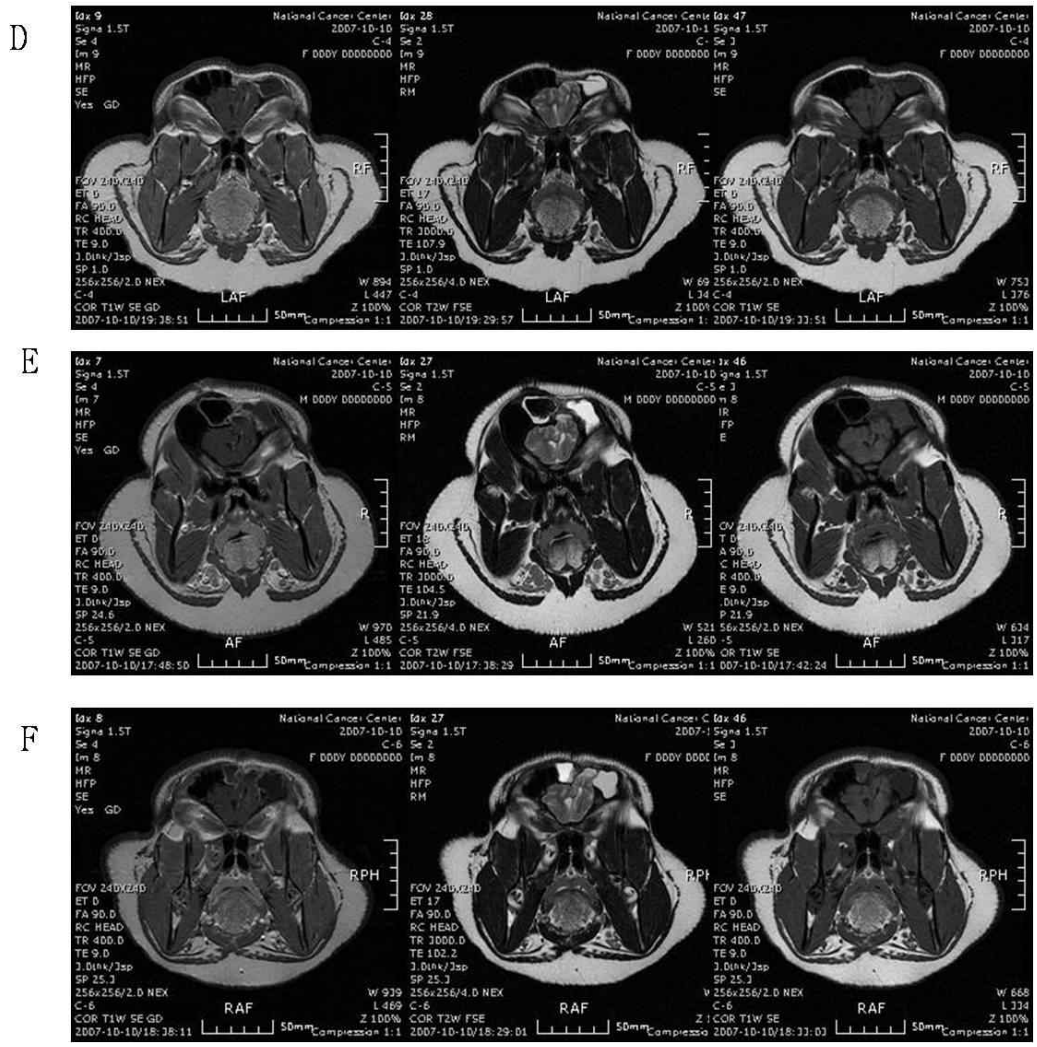

Fig. 8. Follow-up MRI at one month after hyperthermia.

A-F. Coronal T1 (left), coronal T2 (middle), and coronal contrast-enhanced T1 (right) images of pig 6-11, respectively. They have been scheduled to follow MRI at 3 month and 6 month after treatment.

3. 연구결과 고찰 및 결론

고찰

The region of recurrence is generally accepted to be a 2 cm rim around the tumor and therapy should be directed at the tumor and this area. We agree with this but also believe that glioblastoma multiforme is more disseminated disease and metastatic brain lesion is less infilterative than glioblastoma multiforme. There are lots of malignant brain tumors that could be approached and surgically removed to gross total or total removal. There are also many metastatic lesions in the brain which could be removed since they are single lesions or controlled lesions because of improved chemotherapy results. With our hyperthermic system, we can apply hyperthermic treatment after surgical removal of tumor mass, control micro-invasive tumor cells around tumor beds, and then have more chances to control the

local recurrence and to have more survival(quality and quantity) and ultimate care.

Whole brain hyperthermia has the potential advantage of threating distant tumor cells that would otherwise have been unheated by local therapies. But, the possibility of neuronal injury when heating the whole brain must be considered. Many authors refer to the inability of normal neurons to tolerate temperatures greater than 42°C.[1,3] Therefore, optimal dosing, timing, and targeting are needed in hyperthermic treatment. The use of heat as a therapeutic modality is complicated by difficulty achieving even, predictable temperature elevations because different tissues respond to energy sources differently, and blood flow varies from tissue to tissue, from time to time, and as a function of temperature.[4]

In general, however, malignancies within the brain acts as heat sinks. Because of this, regardless of the technique used, it is possible to obtain intratumoral temperatures much above that of the surrounding brain, thereby lessening the risk of brain injury and increasing the chance for successful tumorcidal effects.[5] As same reasons. large gradients in temperature are commonly found at tumor-normal tissue boundaries that possess differential energy absorption, perfusion rates and thermal conductivities.[6] As new applicators for localized hyperthermia are fabricated that are capable of generating tightly focused energy fields, the resulting temperature distributions will become increasingly steep. Similarly, the need for accurate thermometry and precise measurement of elevated temperatures in the tissue will increase. Greater attention concerning the choice of temperature monitoring devices and whether to employ catheters during probe insertion and mapping will become increasingly important in equipment evaluation, thermal dosimetry studies and clinical phase II and III trials.[7]

In this series of experiments, we have used temperature probes which are ideally suited for precise spatial determination of temperature distributions in tissues. These temperature sensors were initially chosen because of their small diameter in size, blunt end rigidity strength along the axial length of the probe. The combination of these properties helped to minimize mechanical damage in the brain tissue.

The results from series of experiments demonstrate that substantial thermal conductive profiles. This study illustrates the thermal distributions of using our hyperthermic system that have steep conductive properties to tissue so as to prevent unintended injuries during high thermal gradients hyperthermia treatment.

The effects of hyperthermic treatment on brain tissue can be viewed in terms of changes in structure and function. In many studies, they considered whether the changes were reversible or permanent. With the brain the major concern was with irreversible function changes, since temporary changes must be a tolerable side effect

During thermal treatment, it is clinically difficult to measure the brain temperature safely and simply, so it is important to infer the brain temperature during hyperthermic treatment. These studies were performed in 11 pigs to exposure the hyperthermic treatment. By utilizing a temperature of 42.5°C of hyperthermic treatment, temperatures recorded from brain parechyme of pigs with thermometry catheter and DITI. We used the thermometry catheters and DITI system to evaluate thermal distribution around hyperthermic probes, and which showed thermal profiles in coincidence. In the experimental animals, the MRI was taken after hyperthermic treatment at 1 month (Pig 3-11) and hostolgic analyses was done for schedule comtpleted animals. The resuts of brain MRI and histolgical analyses were compared. There were tracks remant after hyperthermic treatment, but did not cause damage to surrounding

neurons or white matter. In the review of article, with 43C a partial loss of neurons was seen in the brain tissue adjacent to the temperature probe.[2] The presence of the probe did not enhance the tissue damage around the probe itself. In the white matter, cerebral edema separated the myelin tracks. At temperatures of 44-45C, there was a loss of neurons in either cortical or subcortical gray matter and destruction of myelin tracks in the white matter.[8] After hypterthermic treatment at 42.5°C for 40 minutes with out system, the histological analyses did not show structural destruction of surrounding normal brain, and severe edema in the lesion. Several areas of hyperthermic treatment showed similar findings. The border of the hyperthermic treatment was sharp and non destructive.

Regarding the performance of the hyperthermic system with sphere probe, it can be said that, using heating technique described, it is feasible to reach to therapeutic temperature to malignant brain tumors and metastaic lesions with good clinical result, such as controlled recurrence.

결론

We described the effects of hyperthermia with a newly designed hyperthermic system with sphere probe. We have evaluated the characteristics of newly developed hyperthermic system for clinical trial, and we hope to offer new treatment modality for malignant brain tumors and metastatic lesion. There are lots of mechanisms and clinical results to be evaluated.

In conclusion, this hyperthermic system with sphere probe is a suitable technique for the treatment of brain tumors after surgical removal to control the recurrence. However, a definite mechanisms of hyperthermia and actual result of clinical trial should be shown with further stydy.

4. 연구성과 및 목표달성도

(1) 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

논문명	저자 (저자구분)	저널명(I.F.)	Vol(No)Page	구분	과제 관련성

※저자구분 : 교신, 제1, 공동
※구분 : 국내, 국내 SCI, 국내 SCIE, 국외, 국외SCI, 국외SCIE 등
※과제관련성 : 상(Acknowledgement 가 있는 경우), 중, 하

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역	과제 관련성

※지역 : 국내, 국외

다. 산업재산권

구분	특허명	출원인	출원국	출원번호
발명특허	고온종양치료기	이승훈 외 4인	국내	10-2006-0042451
발명특허	고온종양치료기	이승훈 외 4인	미국,일본, 유럽에 출원	미국11-789059, 유럽 07-008688.9, 일본 2007-124448

※구분 : 발명특허, 실용신안, 의장등록 등

라. 저 서

저서명	저자	발행기관(발행국, 도시)	쪽수	Chapter 제목, 쪽수 (공저일 경우)

마. 연구성과의 정부정책 기여

보고서명	정부정책	기여내용

바. 기타연구성과

(2) 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%)	
				연차	최종
고열종양치료기의 생체역학적인 특성 및 안정성 평가	1차년도	고열종양치료기의 생체역학적 특성에 관한 기본 data구축	순환하는 물의 온도와 종양 치료기로부터의 거리에 따른 뇌조직의 온도에 관한 기본 지식 수립	100	100
		고열종양치료기의 개발	독창적인 물 관류 방식의 고열종양치료기를 개발 고열종양치료기 고정장치 개발		
	2차년도	축적된 data를 바탕으로 고열종양치료기를 개량하고 기구의 조건 및 크기를 다양하게 변화시키고 DITI를 접목시켜 실시간으로 열분포를 감시할 수 있도록 발전시키도록 함	closed sterile system으로 개량하였으며 DITI를 접목하여 치료범위를 확인할 수 있었고 디지털 온도계측 및 flowmeter를 이용하여 정밀한 온도 feedback을 가능하게 하였으며 다양한 크기의 probe를 개발하였다.	100	100
		시술 후 장기간 사육하면서 안정성 평가	3마리의 conventional pig와 6마리의 SPF pig에 시술후 1주일, 1개월, 6개월간 사육하며 신경행동검사 및 MRI촬영, 병리학적 검사를 통해 안정성을 검증함		
	3차년도				

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
동물실험 모델 및 방법의 적합성	돼지를 이용한 동물 실험 모델의 확립
독창적 기전의 고열종양치료기 개발	임상실험을 위한 closed sterile system으로 개량하였으며 다양한 크기의 probe를 개발하였고 온도 monitoring 및 조절장치의 개량을 시행
장기 사육 및 안정성 평가	1주, 1개월, 6개월의 실험동물 사육 및 신경행동검사, MRI 촬영, 병리학적 검사를 통해 안정성을 평가함

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재		Journal of neurosurgery
산업재산권 등록		고온종양치료기로 미국, 일본, 유럽에 발명특허 등록
기 타		

(2) 연구성과의 활용계획

뇌암에 대한 수술중 고열치료법은 악성 뇌종양 및 전이성 뇌종양의 수술후 주변 정상 뇌조직에 침윤되어 종양의 재발을 초래하는 종양세포에 대한 추가적인 치료로서 효과적인 결과를 보일 수 있다. 개발된 고열종양치료기와 동물실험결과 및 안정성을 기반으로 2년의 임상시험을 거쳐 뇌암 및 전이암에 대한 새로운 치료법을 실용화 할 수 있다.

이를 위하여 임상시험을 위한 sterile system의 보완 및 임상시험에 대한 연구가 필요함

6. 참고문헌

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뇌암에대한수술중고열치료법(전임상실험)

국립암센터

1. 이 보고서는 국립암센터 기관고유연구사업 결과보고서입니다.

2. 이 보고서 내용을 인용할 때에는 반드시 국립암센터 연구사업 결과임을 밝혀야 합니다.