Chap. 8-1
HIFU Therapeutic Technology

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重点和难点

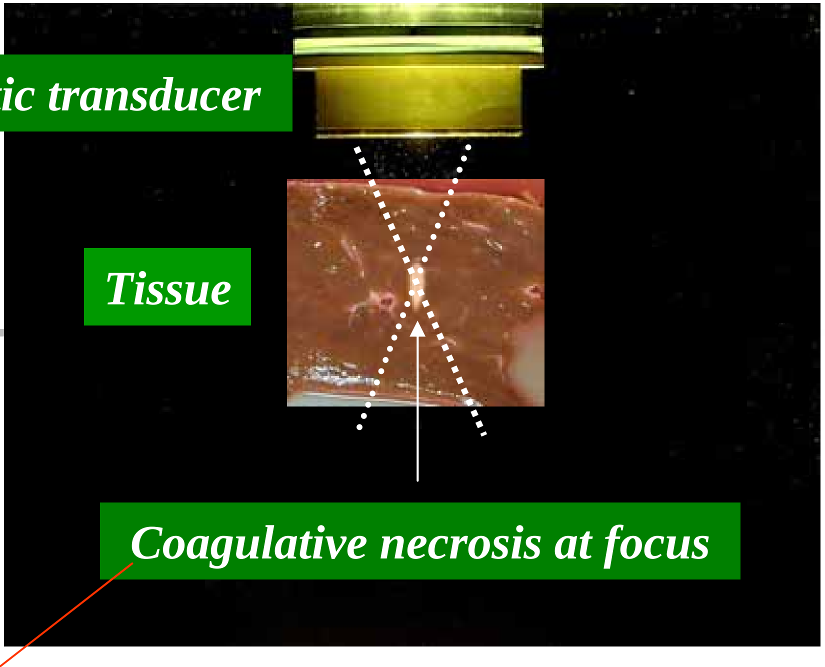
1. HIFU的原理、技术的特征。
2. HIFU治疗机制。
3. HIFU 治疗设备。
4. 影响聚焦超声换能器的参数，如何影响。
5. 影响HIFU生物学效应的因素，如何影响。
6. 监控HIFU的影像技术有哪些，监控的基础是什么。
7. 临床方案。

Thermal therapies ….

“Those diseases that medicines do not cure are cured by knife. Those that the knife does not cure, are cured by fire, and those that fire does not cure must be considered incurable”

Hippocrates (400 B.C.)

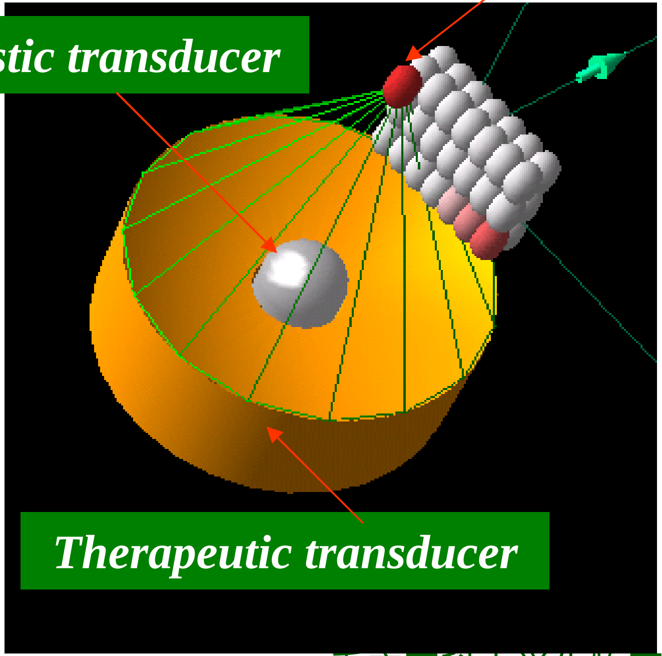
HIFU noninvasive ablation of tumor lesion



Therapeutic transducer

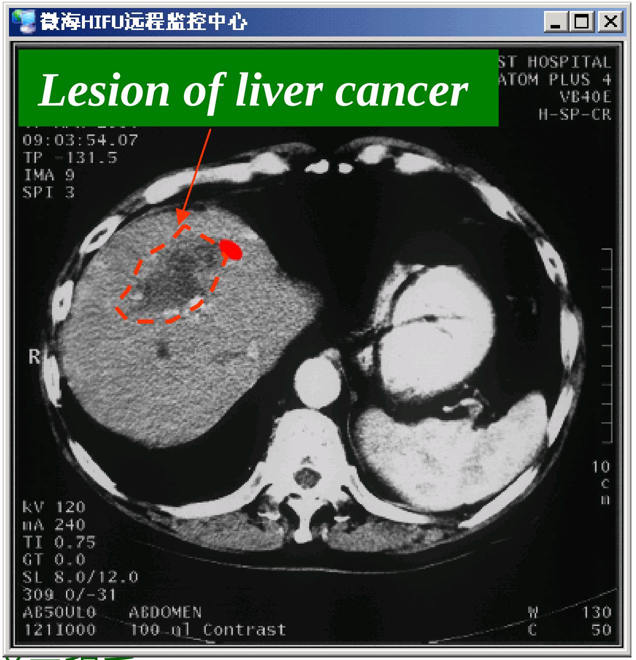
Tissue

Coagulative necrosis at focus



Diagnostic transducer

Therapeutic transducer



Lesion of liver cancer

History of HIFU

- ❑ 1927–Wood and Loomis: biological effects of high-intensity ultrasound
- ❑ 1942–Lynn et al: potential applications of HIFU
- ❑ 1954–William Fry *et al*: lesions in brains of cats and monkeys
- ❑ 1958–Frank Fry: system for treatment Parkinson’s disease

-----interest in HIFU then diverted to other applications.

- ❑ 1956–Burov: high-intensity ultrasound as cancer treatment

-----For 3 decades -much independent research into wider applications.

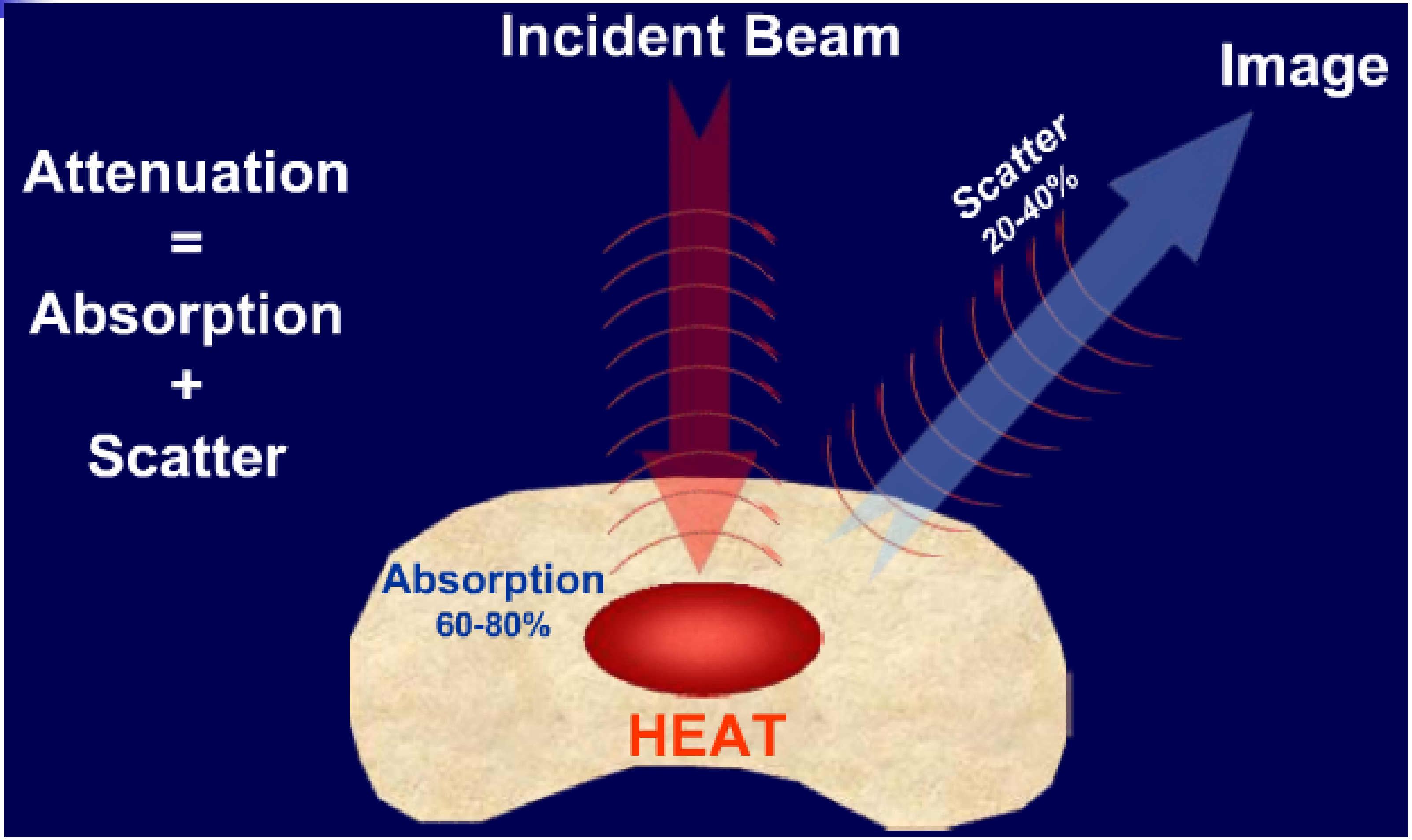
- ❑ 1993/4–First reports of clinical use to target prostate (BPH/Ca)
- ❑ 1997 –First clinical treatment of liver cancer, breast cancer, bone tumour in China.

Technical Aspects of HIFU

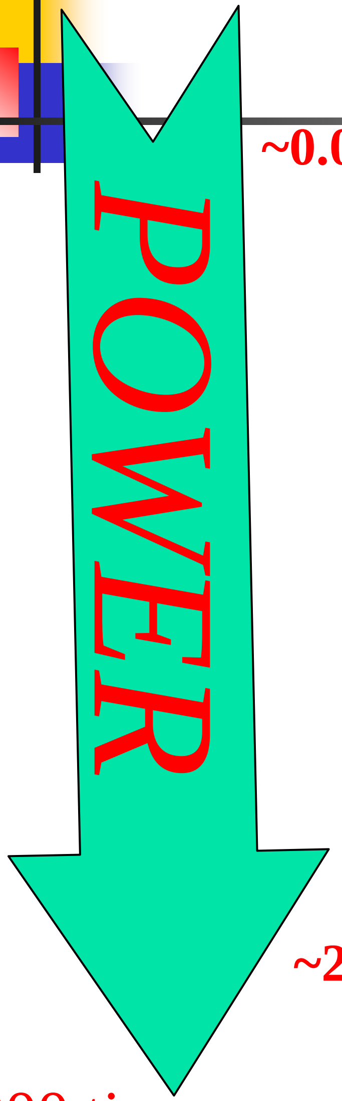
What is HIFU?

- High energy (intensity) ultrasound beam.
- Brought to tight focus at a distance from source.
- Absorption of energy leads to tissue heating.
- Causes very localized temperature rise at focus.
- Sharply demarcated area of coagulative necrosis.
- No damage to overlying and surrounding tissue.
- Ideal for manipulation as noninvasive tool.

Ultrasound (in tissue)



Ultrasound (Intensity or Power)



~0.02W

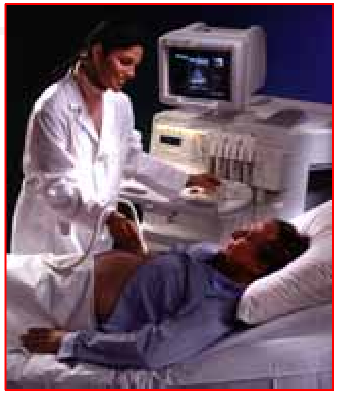
~200W

10,000 times more energy

DIAGNOSIS:

Tissue information

Without biological effect



THERAPY:

Deliberate (beneficial)

biological effect

(reversible or irreversible)

Functional modification

SURGERY:

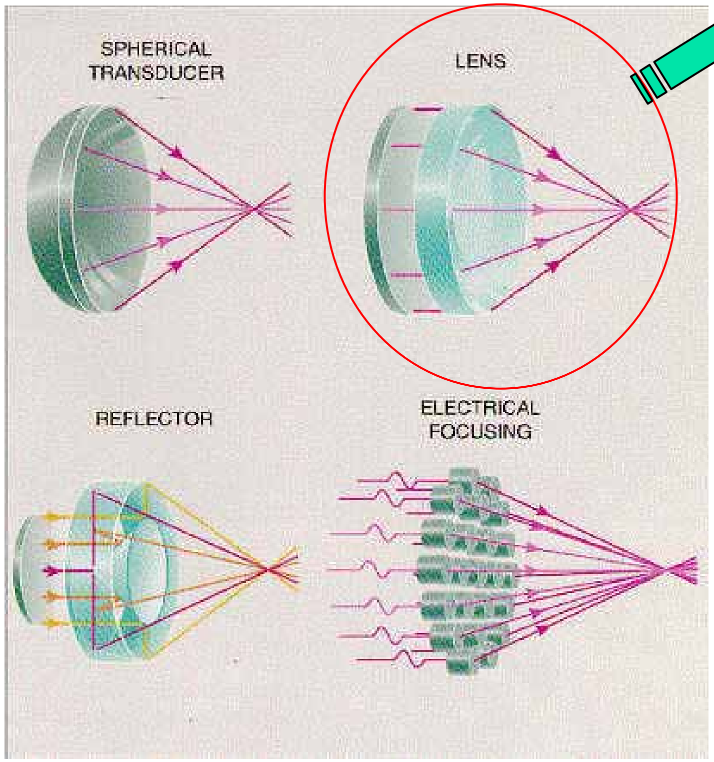
Cell killing

Table 14.1 Output characteristics of ultrasound devices

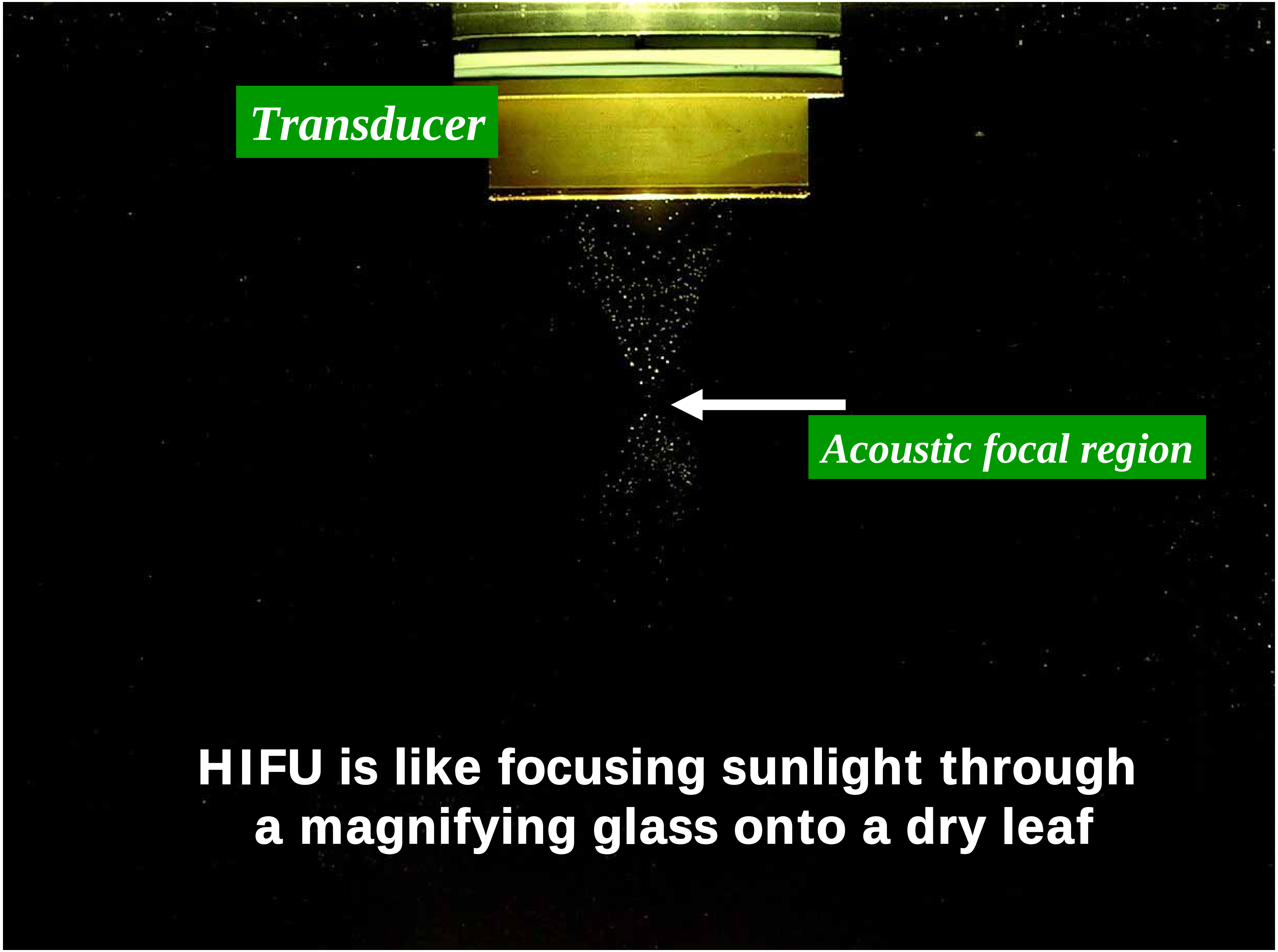
Equipment Type	Frequency range (MHz)	Typical source area (mm^2)	Typical duty factor	Power (mW)	external probes		intra-cavitary probes	
					Spatial peak, temporal average Intensity I_{spta} (mW cm^{-2})	peak negative acoustic pressure p^- (MPa)	spatial peak, temporal average intensity I_{spta} (mW cm^{-2})	peak negative acoustic pressure p^- (MPa)
Diagnostic								
Pulse-echo								
B-mode	1-20	100-3000	0.001	4-256(64)	1-1330(175)	0.45-5.54(2.09)	0.8-284(64.60)	0.66-3.5(2.32)
M-mode	1-20	100-3000	0.001	0.5-213(46)	4.2-6.04(127)	0.45-5.54(2.09)	2.0-210(62.7)	0.66-3.5(2.32)
Doppler								
Fetal heart detector	2-4	100	1	5-30		0.01		
Pulsed Doppler	5-10	100	0.01	11-324(144)	36-9080(1570)	0.67-5.32(2.18)	97.1-1440(747)	0.97-3.53(2.26)
Colour flow	5-10	100	0.01	35-295(138)	21-2150(429)	0.46-4.25(2.41)	0.97-3.53(2.26)	1.14-3.04(2.47)
Therapeutic								
Physiotherapy								
Continuous wave	0.75-3	300	1	0-15000				
Pulsed	0.75-3	300	0.2	0-3000	500	0.5		
Surgery	0.5-10	5000	1	200000		5		

Source: from Henderson et al.(1995) and Whittingham (2000).

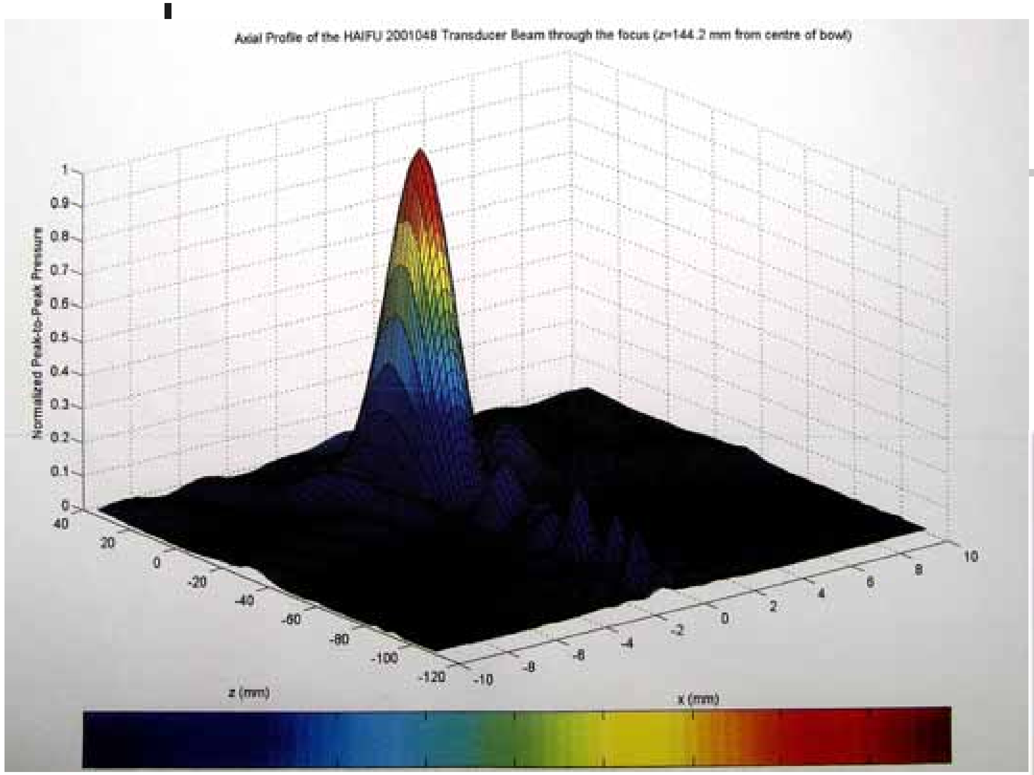
Ultrasound (Focusing)



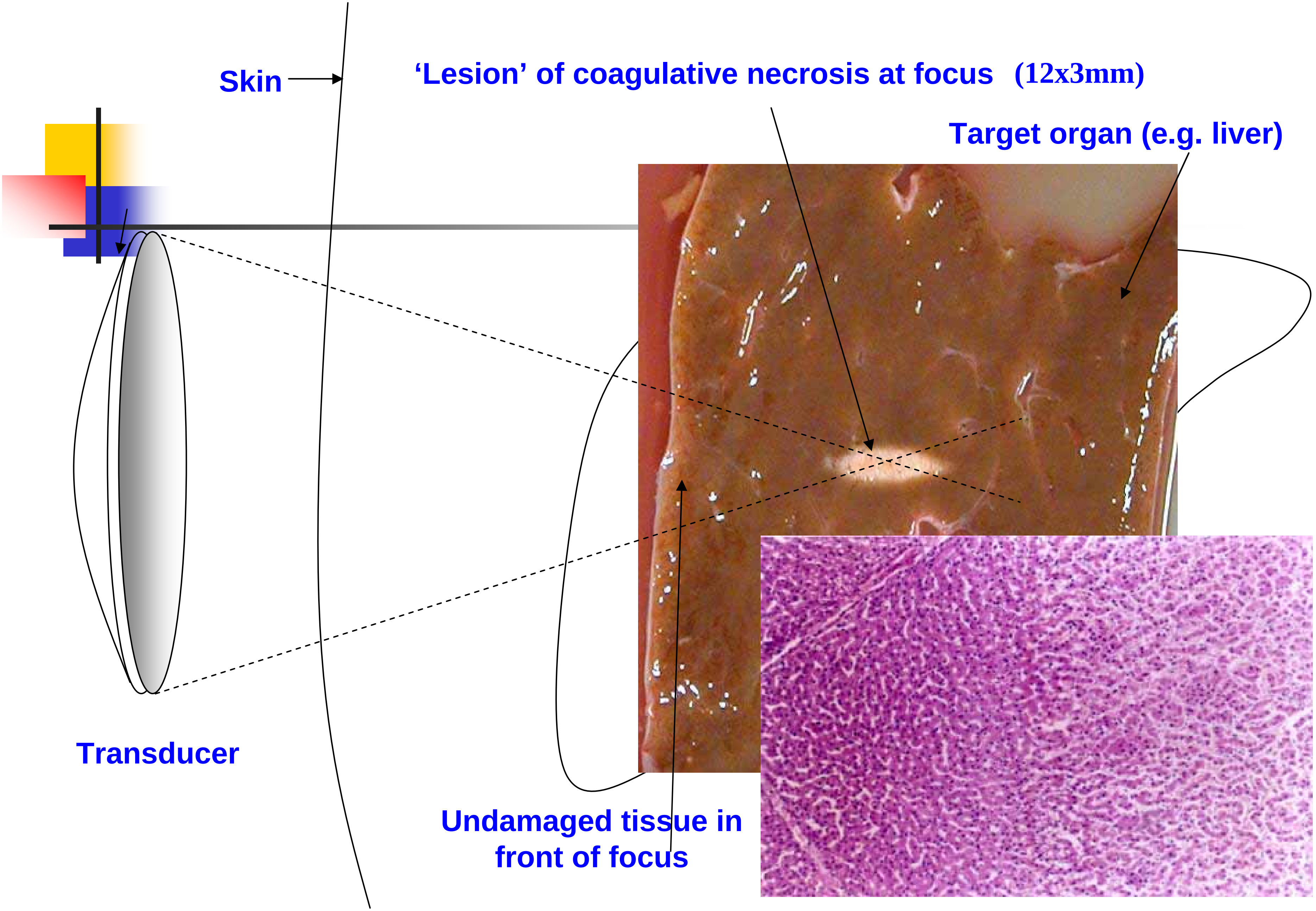
Ultrasound beams may be focused by curving the piezoelectric plate or by interposing a lens or reflector between a flat plate and the target. A phased array of transducers is focused electronically.



HIFU is like focusing sunlight through a magnifying glass onto a dry leaf



0.8MHz 120mm 135mm



Skin

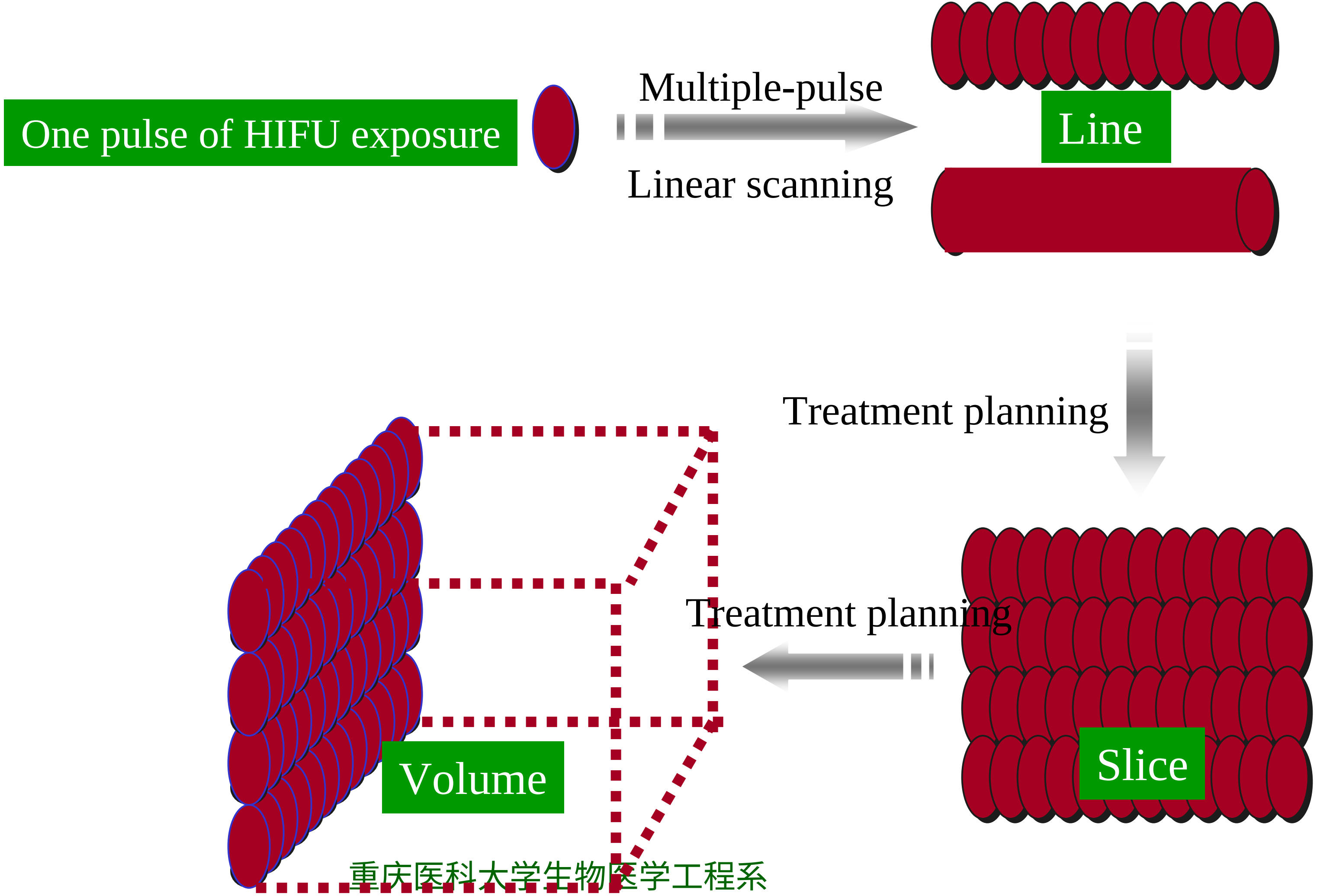
‘Lesion’ of coagulative necrosis at focus (12x3mm)

Target organ (e.g. liver)

Transducer

Undamaged tissue in front of focus

HIFU 3D therapeutic plan



One pulse of HIFU exposure

Multiple-pulse

Linear scanning

Line

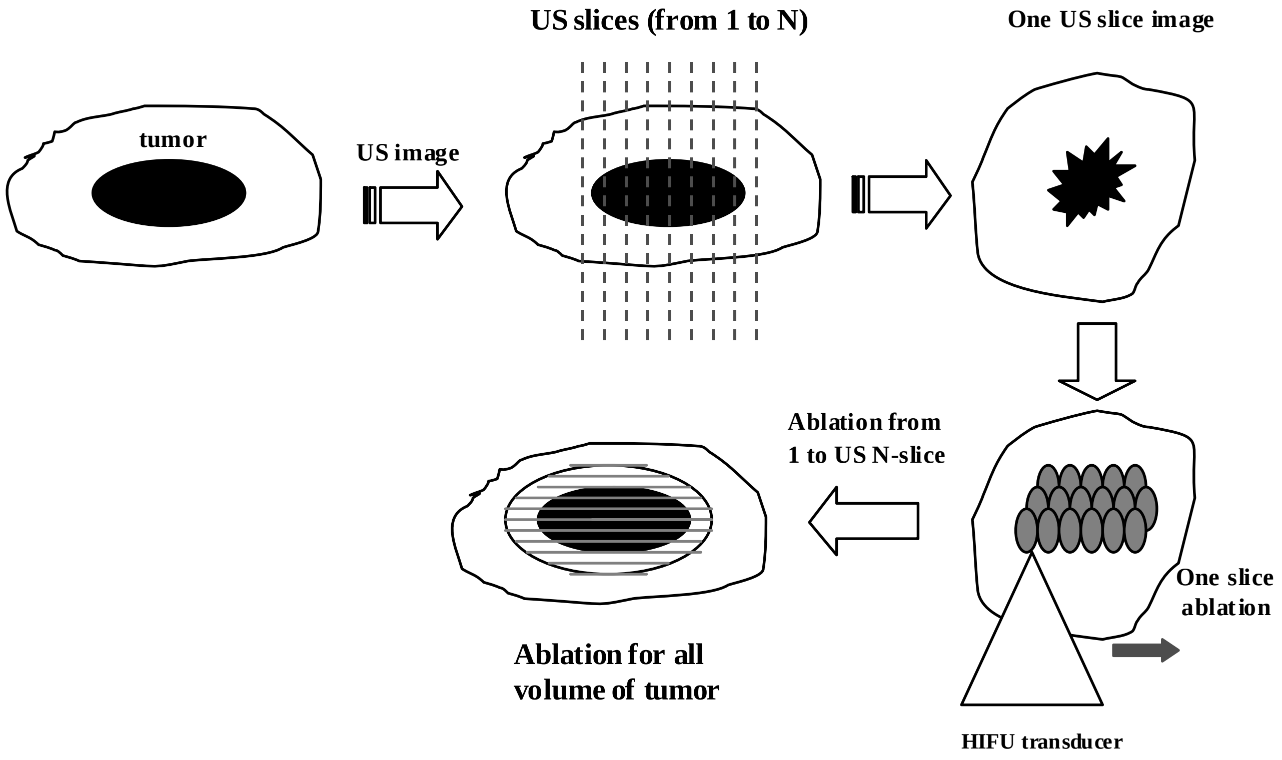
Treatment planning

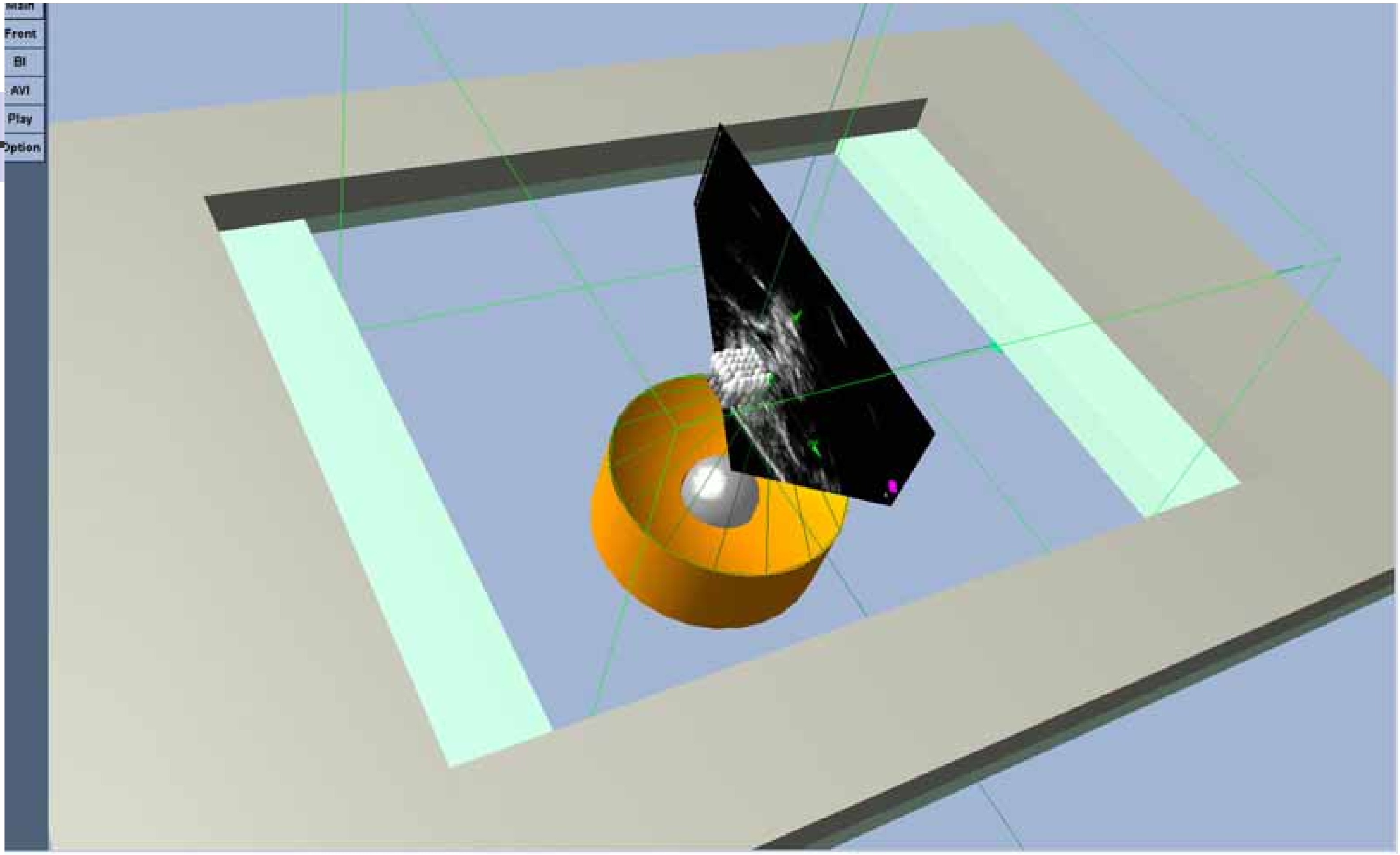
Slice

Treatment planning

Volume

HIFU 3D Conformal Ablation





3D Reconstruction of Scanning Tracks of BFR

Movie of BFR → Line →Slice → Volume

Image Guidance

- Planning
- Targeting
- Monitoring
- Controlling
- Assessing tumour response

Image Monitoring

- US imaging (Hyperechoic change within ablated tissue)
- MRI (Temperature measurement within ablated tissue)

Real-time ultrasound-guided HIFU system

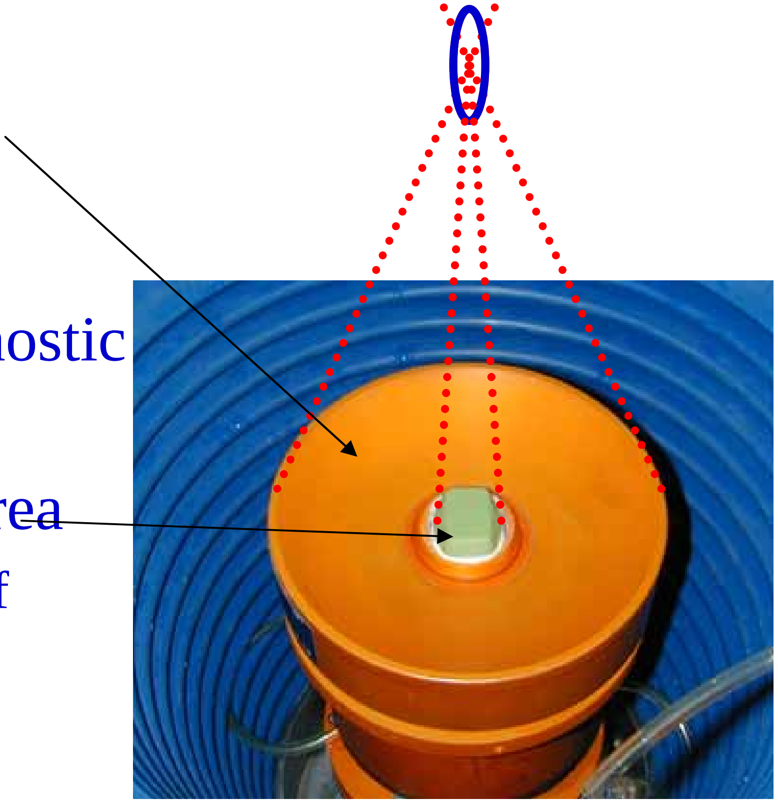
Transducer

- Plane transducer with integral aluminium lens

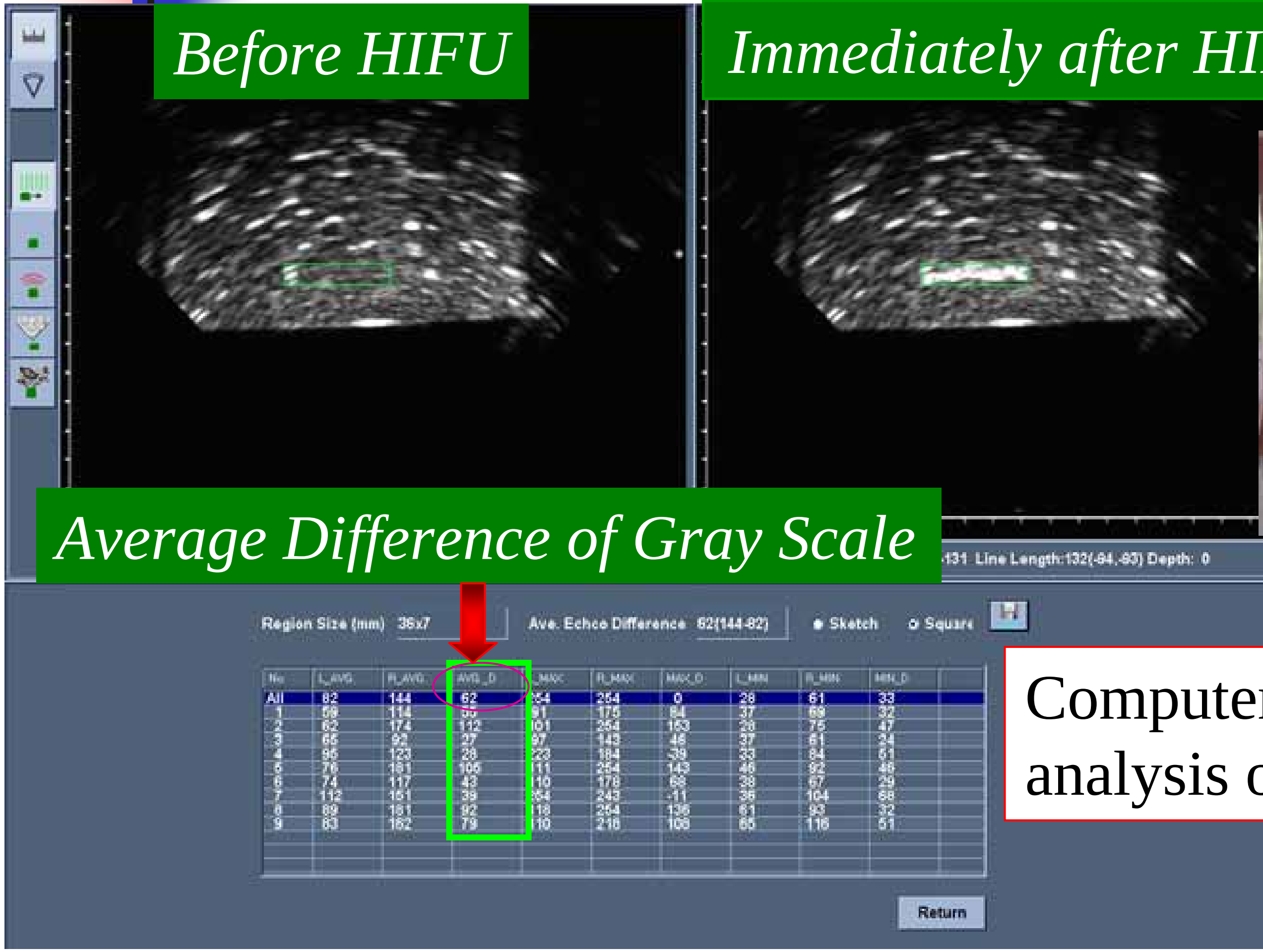
Imaging

- Built-in coaxial 3.5 MHz diagnostic transducer
- Real-time imaging of treated area

  (using computer assisted analysis of grey-scale changes)



Real Time US Image Monitoring



Before HIFU

Immediately after HIFU

Average Difference of Gray Scale

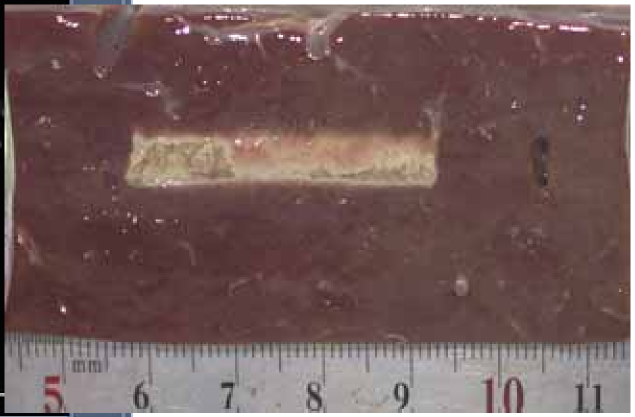
-131 Line Length:132(-94,-83) Depth: 0

Region Size (mm) 36x7

Ave. Echo Difference 62(144-82)

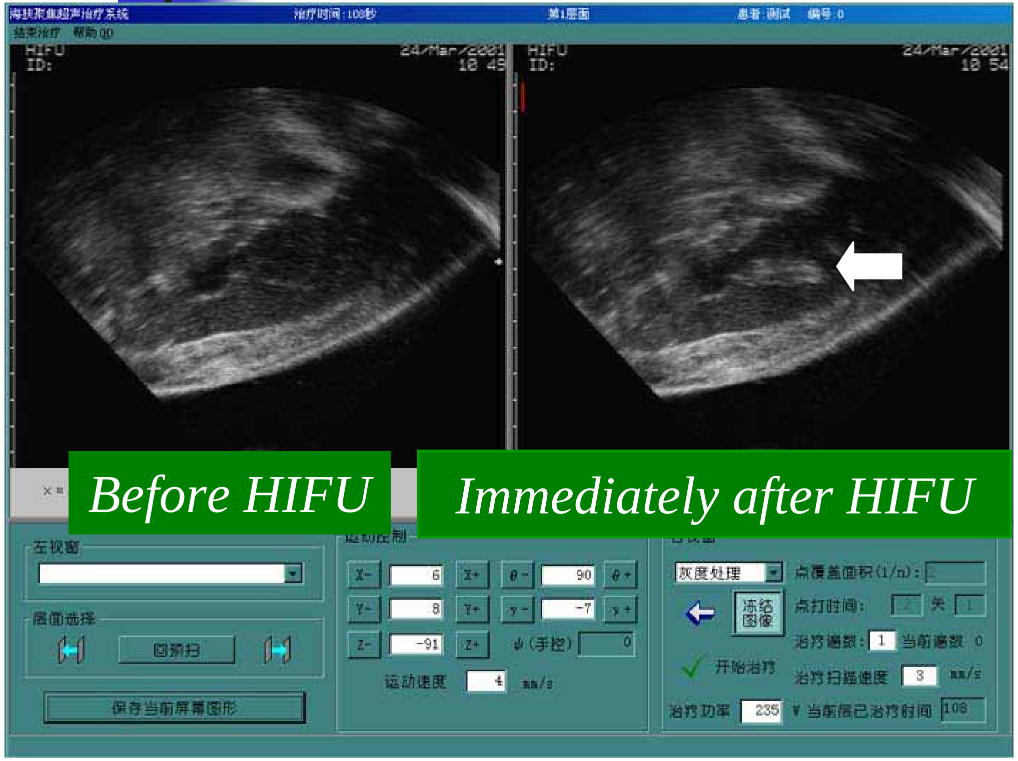
● Sketch ○ Square

No	L_AVG	R_AVG	AVG_D	L_MAX	R_MAX	MAX_D	L_MIN	R_MIN	MIN_D
All	82	144	62	254	254	0	28	61	33
1	59	114	55	91	175	84	37	69	32
2	62	174	112	101	254	153	28	75	47
3	65	92	27	97	143	46	37	61	24
4	95	123	28	223	184	-39	33	84	51
5	76	181	105	111	254	143	46	92	46
6	74	117	43	110	178	68	38	67	29
7	112	151	39	254	243	-11	36	104	68
8	89	181	92	118	254	136	61	93	32
9	83	162	79	110	218	108	65	116	51

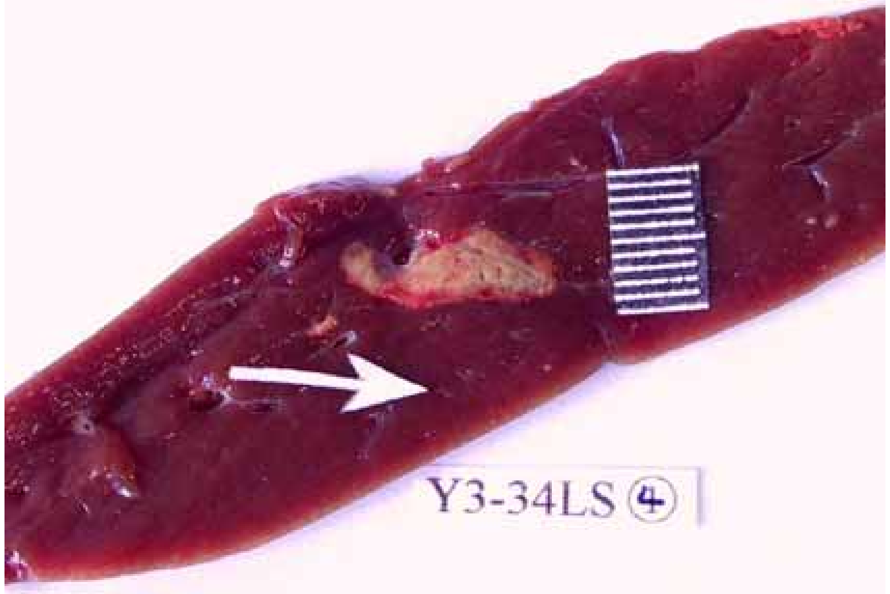


Computer assisted quantitative analysis of gray-scale changes

Real Time US Image Monitoring

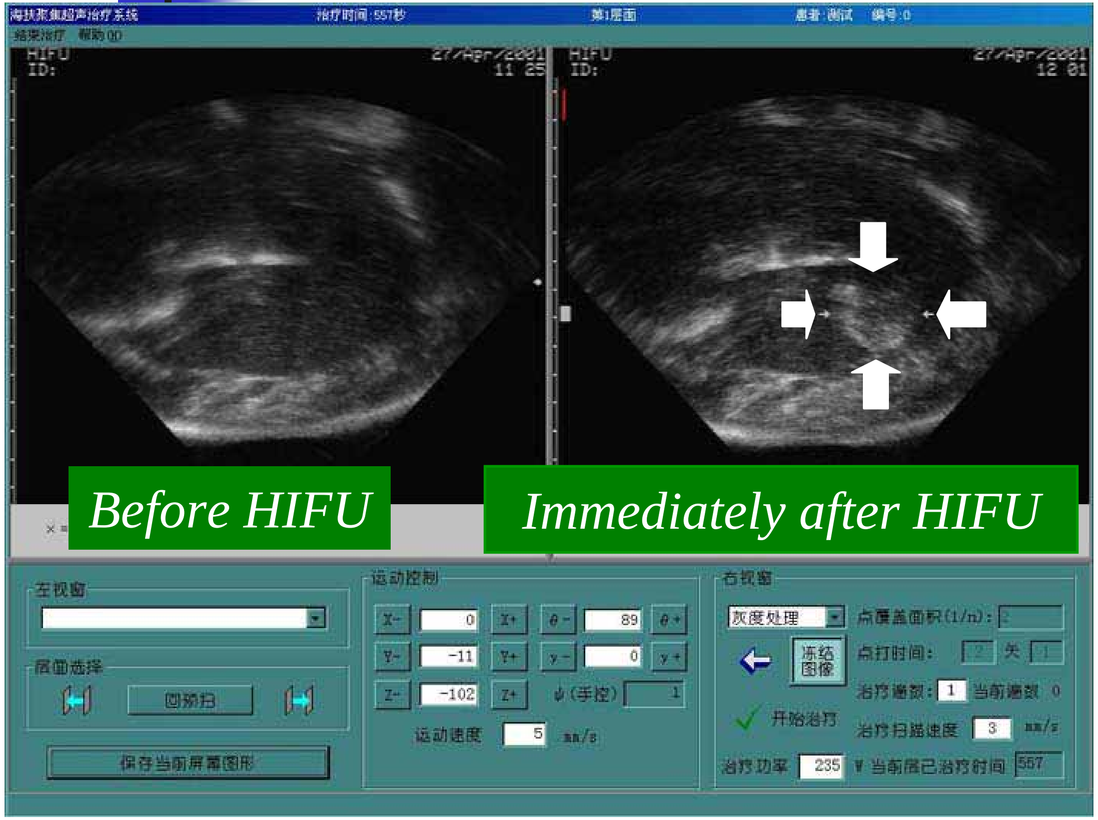


X: 6
Y: 8
Z: -91
θ: 90
y: -7
ψ（手控）: 0
运动速度: 4 mm/s
灰度处理
点覆盖面积(1/n):
点打时间:
治疗遍数: 1 当前遍数 0
治疗扫描速度: 3 mm/s
治疗功率: 235 V
当前层已治疗时间: 108



Real time visualization of coagulative necrosis in *in vivo* goat liver on the US image immediately after one linear HIFU scanning

Real Time US Image Monitoring


海扶聚焦超声治疗系统　治疗时间:557秒　第1层面　患者:测试　编号:0

X: 0　Y: -11　Z: -102　θ: 89　γ: 0　ψ(手控): 1

运动速度: 5 mm/s

点覆盖面积(1/n): 2

点打时间: 2　关 1

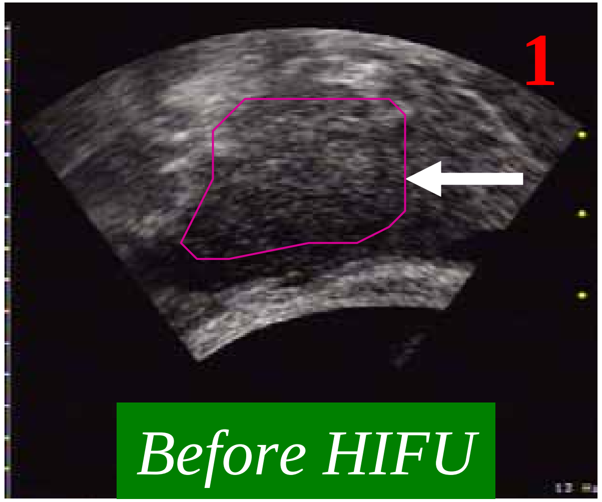
治疗遍数: 1　当前遍数 0

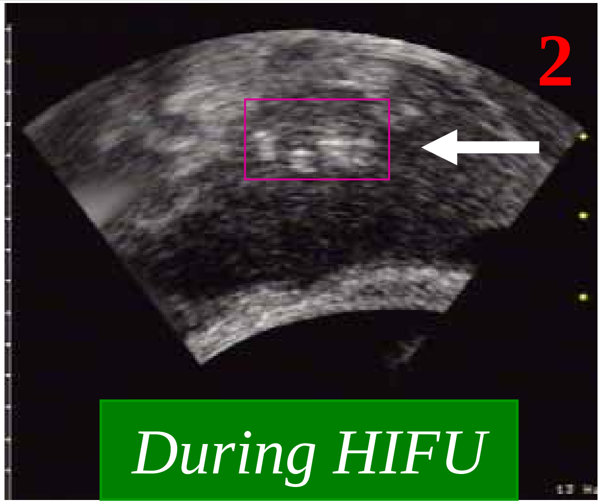
治疗扫描速度: 3 mm/s

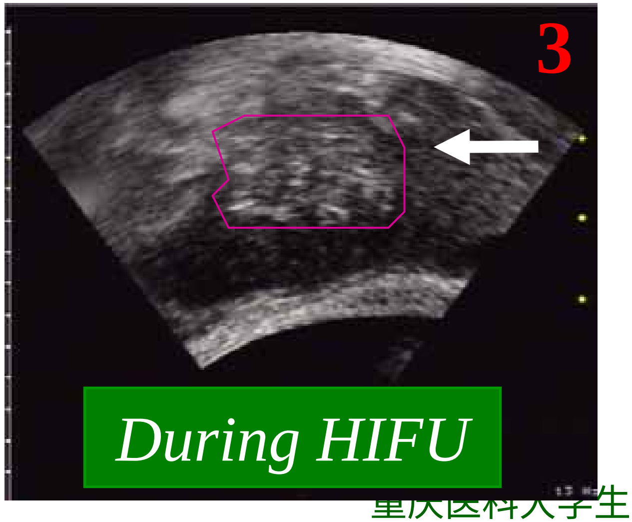
治疗功率: 235 W　当前层已治疗时间: 557

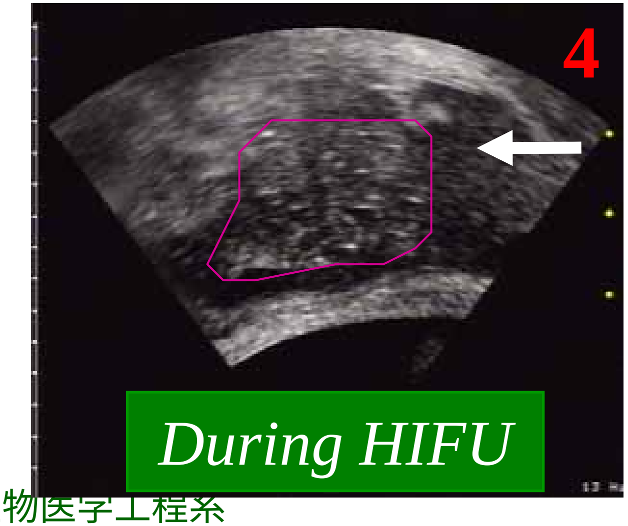
Real time visualization of coagulative necrosis in *in vivo* goat liver on the US image immediately after multiple linear HIFU scanning

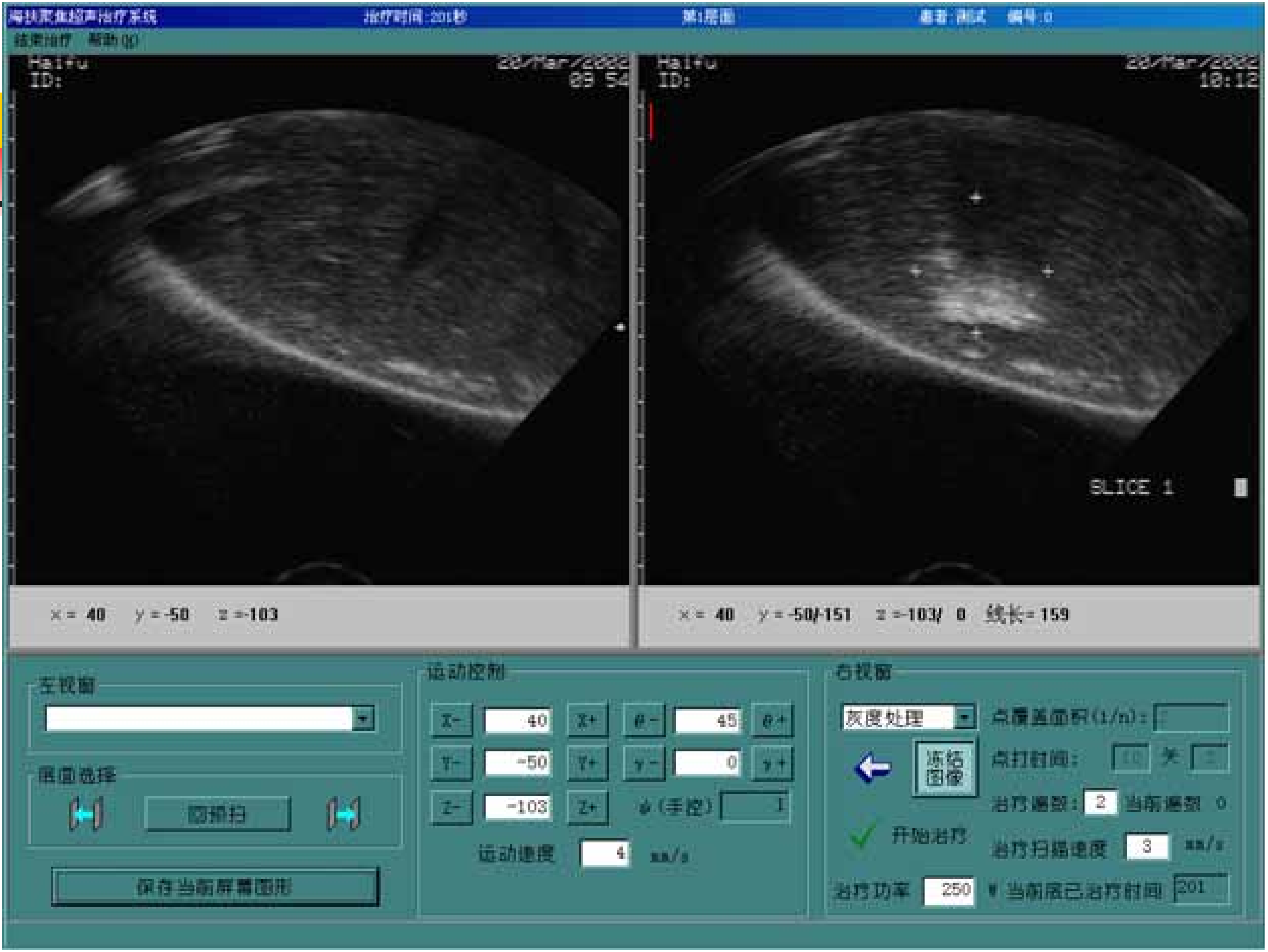
Real Time US Image Monitoring











海扶聚焦超声治疗系统 治疗时间:201秒 第1层面 患者:测试 编号:0

Haifu ID: 28/Mar/2002 09 54

Haifu ID: 28/Mar/2002 10:12

SLICE 1

x = 40 y = -50 z = -103

x = 40 y = -50/-151 z = -103/ 0 线长 = 159

运动控制

X 40

Y -50

Z -103

θ 45

γ 0

ψ (手控) 1

运动速度 4 mm/s

右视窗

灰度处理

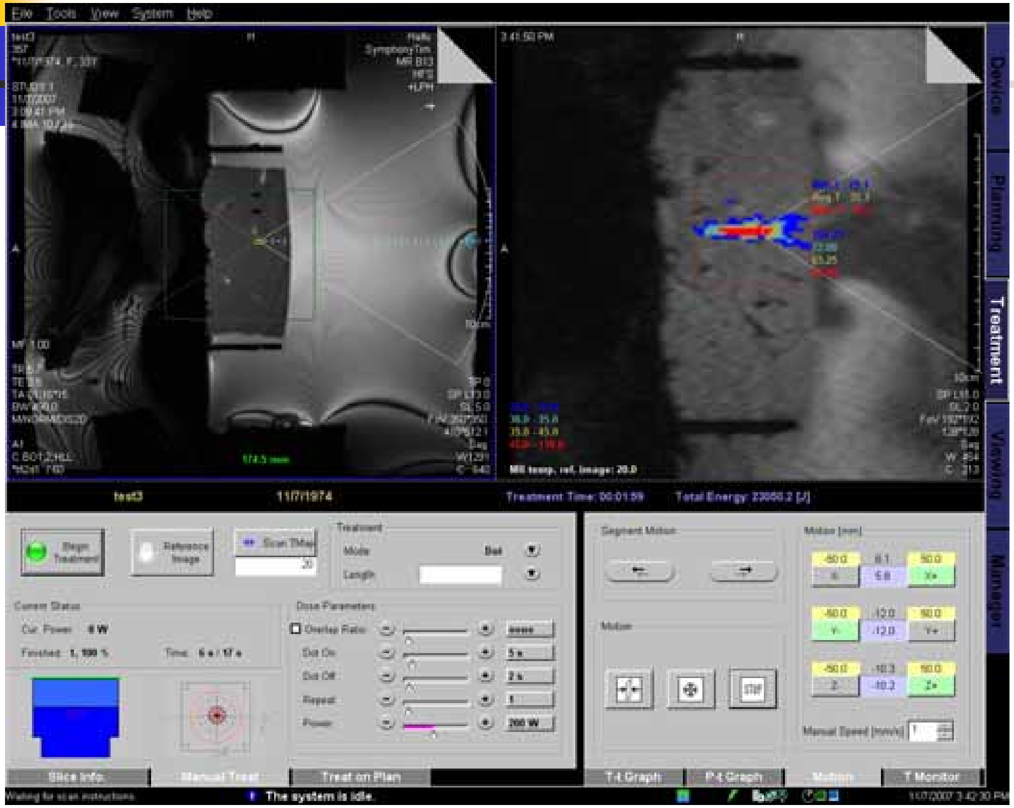
治疗遍数: 2 当前遍数 0

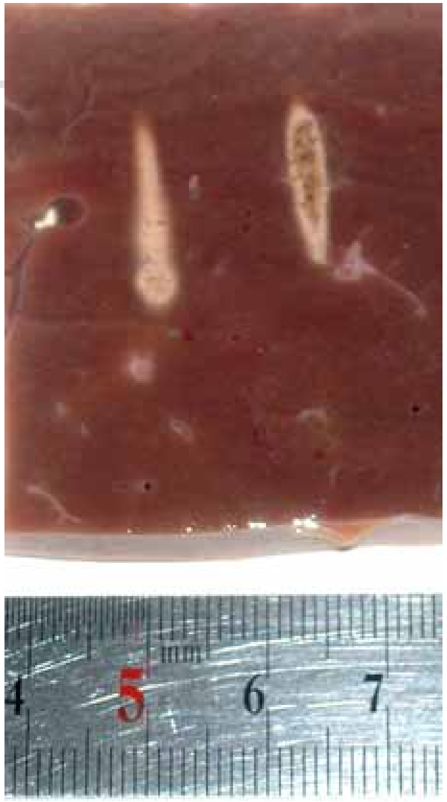
治疗扫描速度 3 mm/s

治疗功率 250 W 当前层已治疗时间 201

A Prototype MRgHIFU Therapeutic System

Real Time MRI Monitoring

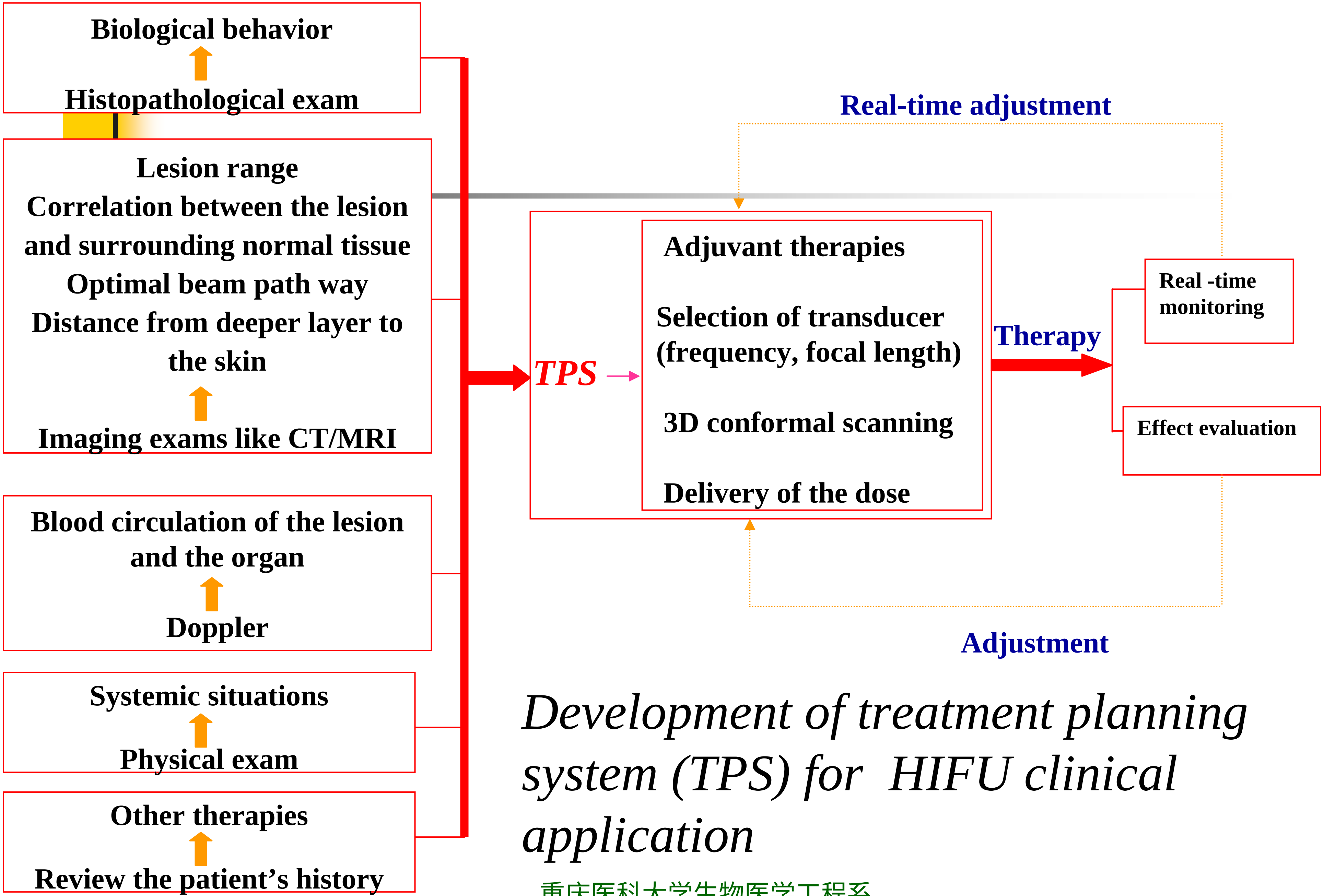




Real time visualization of a single lesion in *in vitro* ox liver on the MRI T-map imaging during HIFU

Features

	US	MRI
Cost effective	🟥	
3D anatomic information for exact tumor targeting	🟥	🟥
Beam path visualization for safe treatment	🟥	🟩
Real time thermometry to achieve planned outcome	🟩	🟥
Post-treatment contrast imaging for evaluating treatment outcome	🟩	🟥
Motion robust (correction, tracking)	🟥	🟩



Biological behavior

Histopathological exam

Lesion range
Correlation between the lesion and surrounding normal tissue
Optimal beam path way
Distance from deeper layer to the skin

Imaging exams like CT/MRI

Blood circulation of the lesion and the organ

Doppler

Systemic situations

Physical exam

Other therapies

Review the patient’s history

TPS

Adjuvant therapies

Selection of transducer (frequency, focal length)

3D conformal scanning

Delivery of the dose

Real-time adjustment

Therapy

Real -time monitoring

Effect evaluation

Adjustment

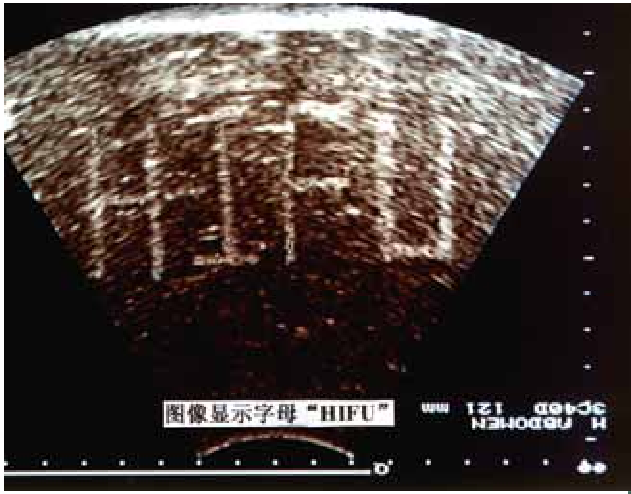
Development of treatment planning system (TPS) for HIFU clinical application

Three Characteristics of HIFU Tumor Ablation

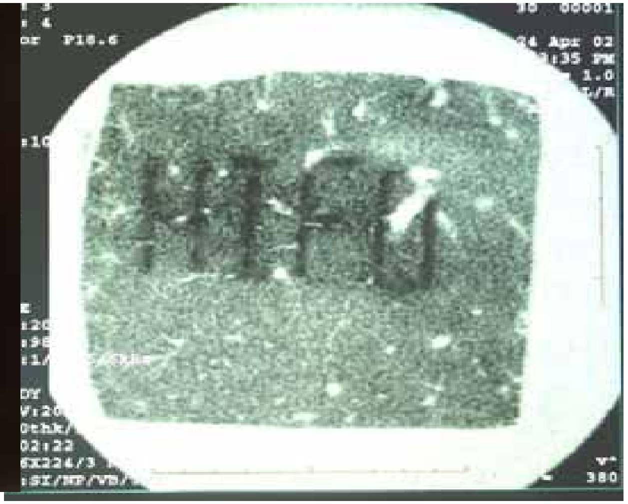
- ☐ Noninvasive thermal ablation
- ☐ Thermal ablation of tumor at any shape
- ☐ Real-time imaging monitoring

That is HIFU!

Gross shape of “HIFU” with basic units of HIFU-induced BFR



The ultrasound-imaging of “HIFU”



The MRI –imaging of “HIFU”

HIFU Therapy Device

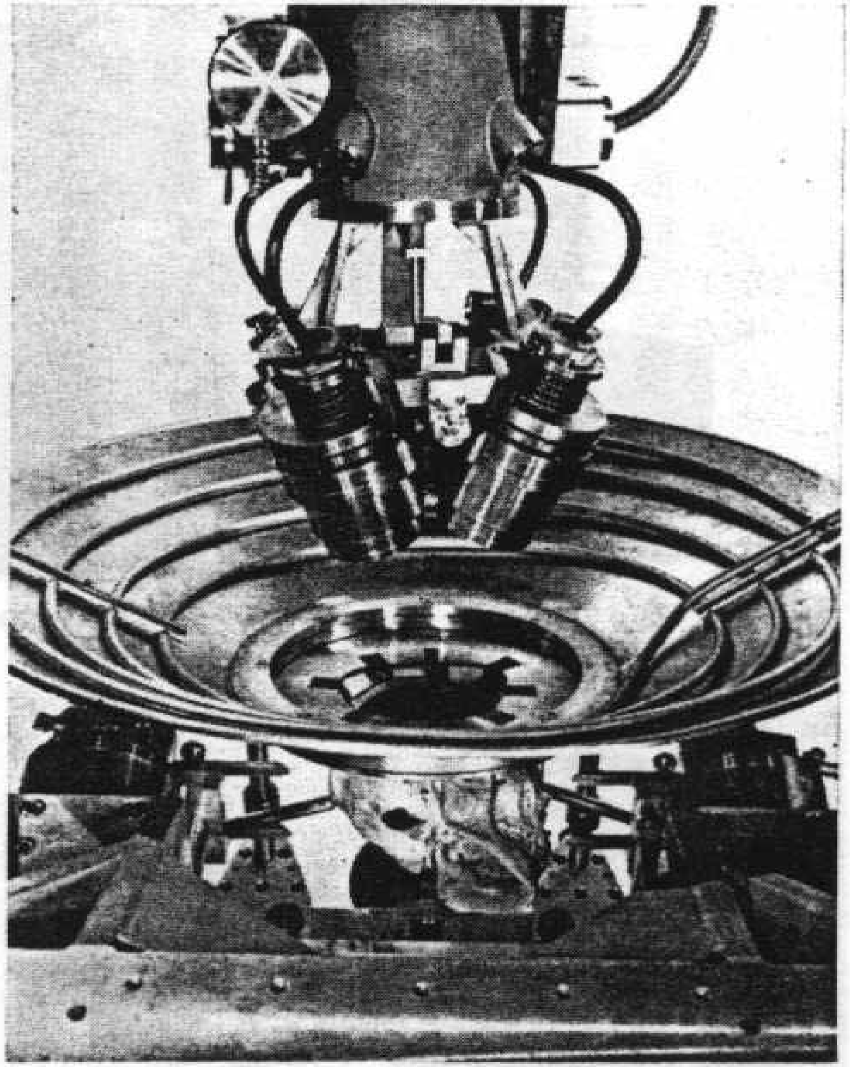
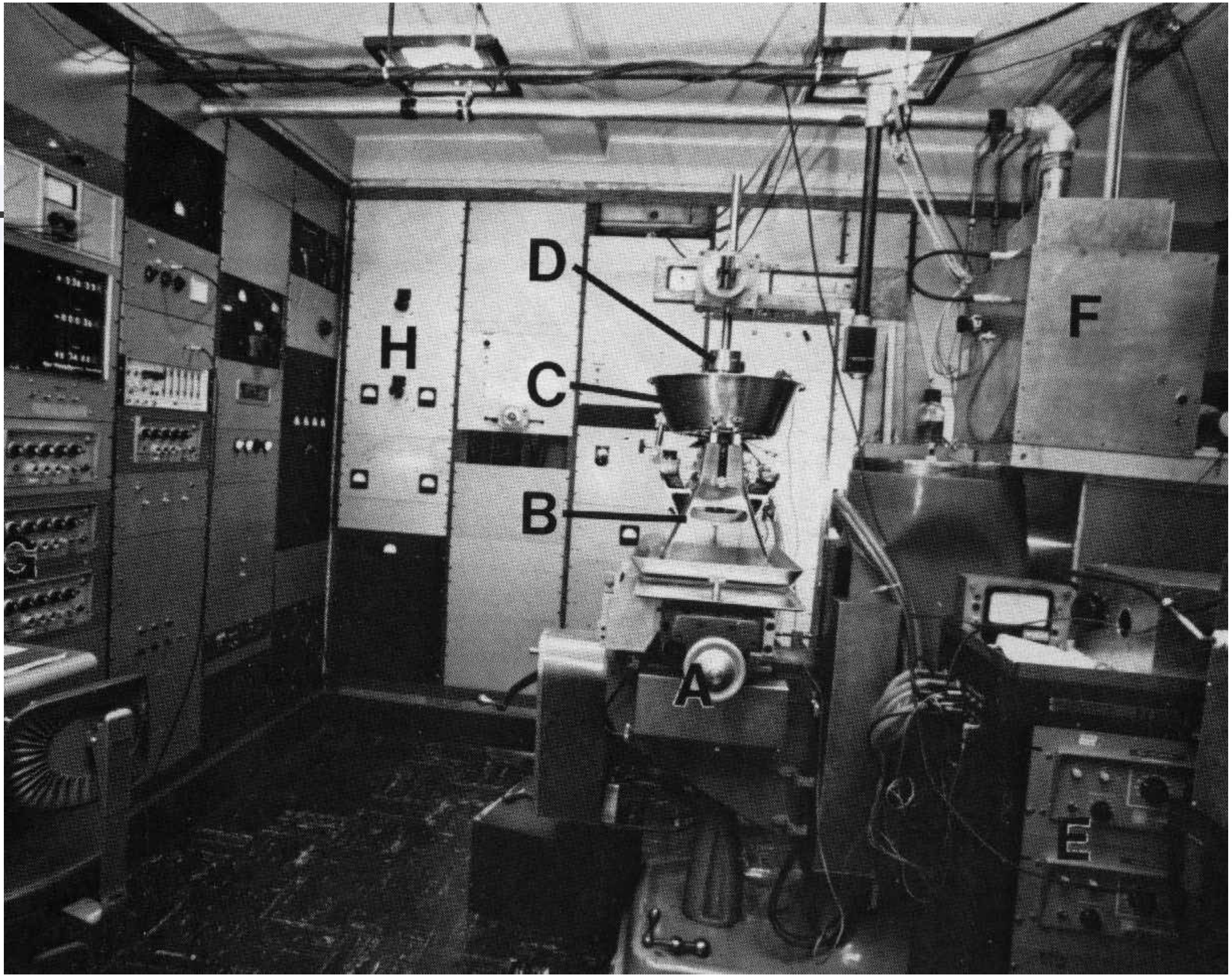


FIG. 4. 4-Beam focusing transducer for use in human neurosurgery.

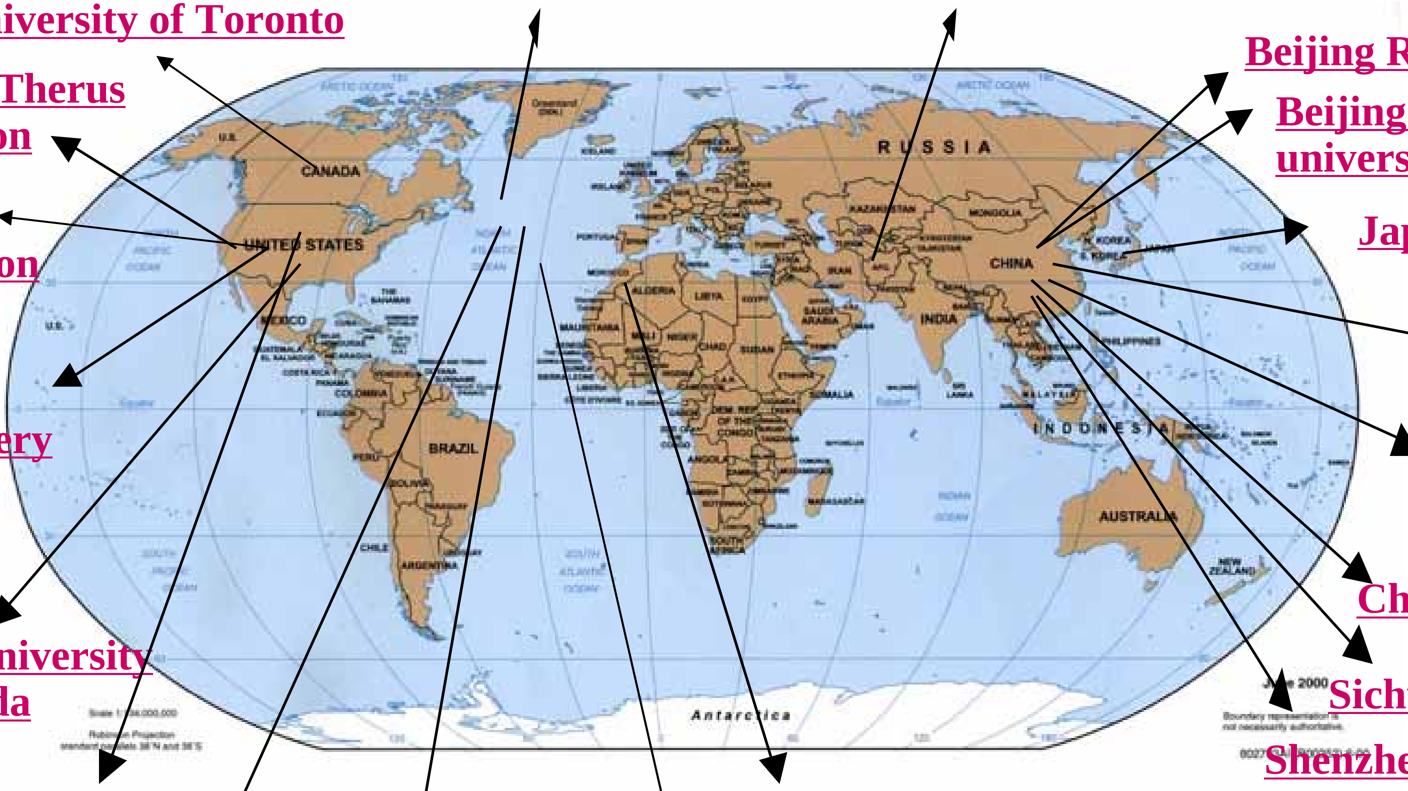
Fry *et al*



Experimental system used by Fry and Fry in Illinois

Types of Device

- Transrectal /Extracorporeal
- Ultrasound / MRI guidance



Royal Marsden Hospital

Inserm

University of Toronto

Beijing Redesheng

American Therus Corporation

Beijing Medical university

University of Washington

Japan

Shanghai Aishen

American Focus Surgery

Nanjing University

Chongqing Haifu

American University of Minnesoda

Sichuan Mianyang

Shenzhen

Harvard

Israel-based InSightec

EDAP

France-based IMSONIC

Heidelberg

First Experiment Device

1988

Second Experiment Device

1992

Third Experiment Device

1994

The Prototype

1996

The Commercialized Machine

1999

Model JC Focused Ultrasound Tumor Therapeutic System

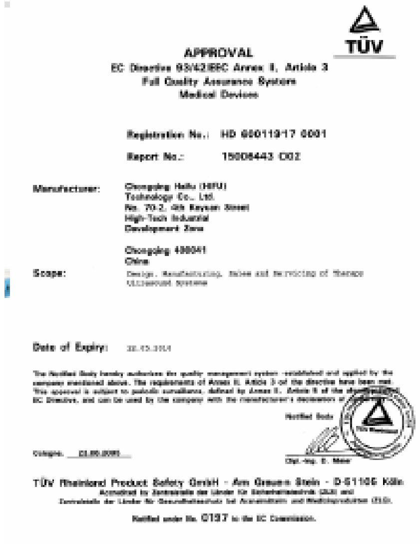
中华人民共和国
医疗器械注册证

Obtained production license in 1999

CERTIFICATE
The TÜV CERT Certification Body
of TÜV Anlagentechnik GmbH

Chongqing HIFU Technology Co., Ltd.

Obtained ISO9001 and EN46001 quality system attestation which is awarded by laiyin co. of Germany.



TÜV

APPROVAL
EC Directive 93/42/EEC Annex II, Article 3
Full Quality Assurance System
Medical Devices

Registration No.: HD 60011917 0001

Report No.: 15008443 002

Manufacturer: Chongqing Haifu (HIFU)
Technology Co., Ltd.
No. 70-2, 4th Keyuan Street
High-Tech Industrial
Development Zone

Chongqing 400041
China

Scope: Design, Manufacturing, Sales and Servicing of Therapy Ultrasound Systems

Date of Expiry:

Notified Body

TÜV Rheinland Product Safety GmbH - Am Grauen Stein - D-51105 Köln

Notified under No. 0197 to the EC Commission.

CE approval

Obtained international patents

Brevet canadien / Canadian Patent

2,206,703

Canada

ПАТЕНТ

№ 2210409

Russia

United States Patent and Trademark Office

NOTICE OF ALLOWANCE AND FEE(S) DUE

RECEIVED

JUL 29 2003

USA

K. L. TAN & ASSOCIATES

INVOICE

Singapore Patent Application Number 200004113-7
"A High Intensity Focused Ultrasound System For Scanning And Curing Tumor"
Chong Qing HIFU Technology Co., Ltd.

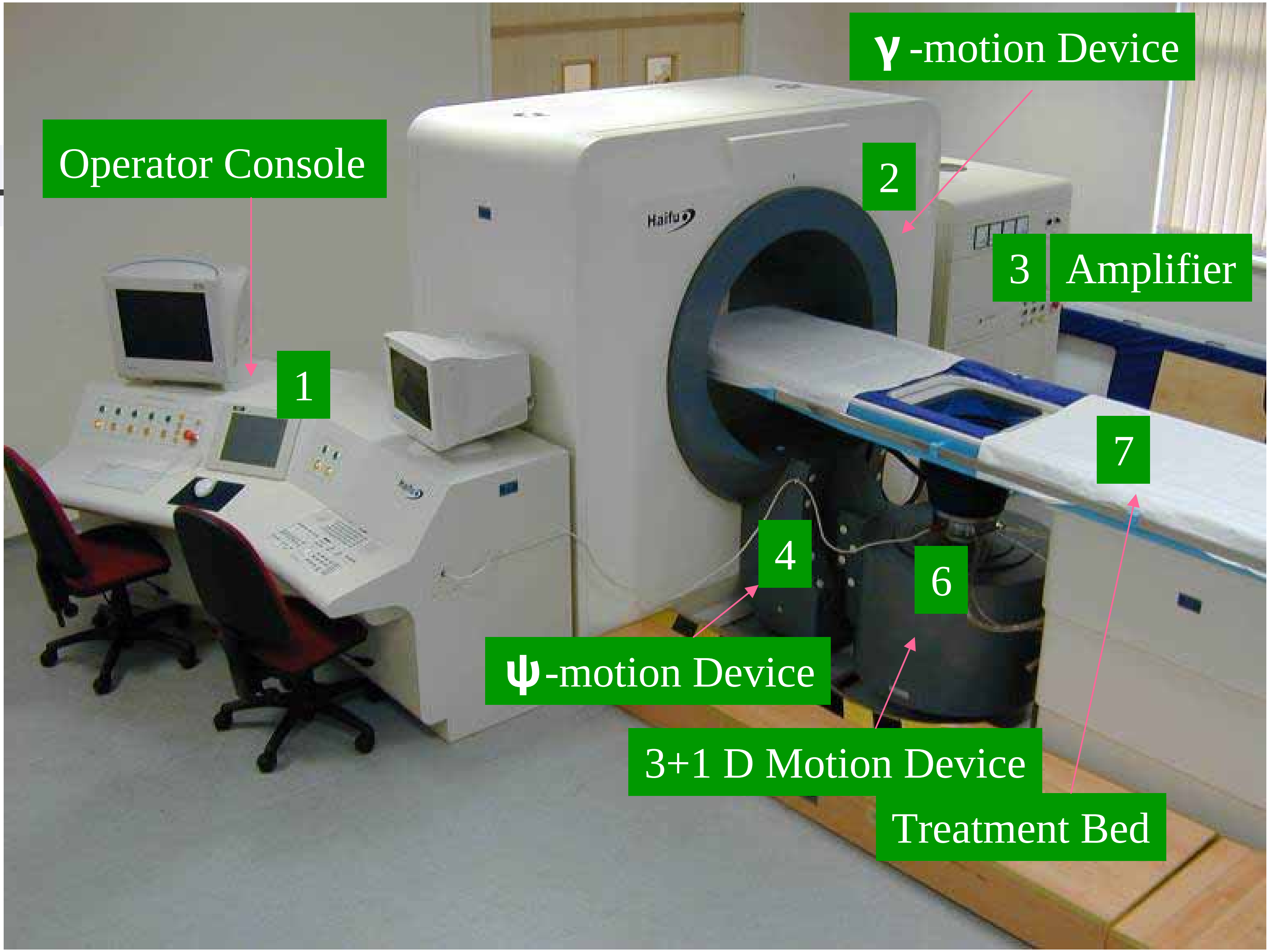
DISBURSEMENTS

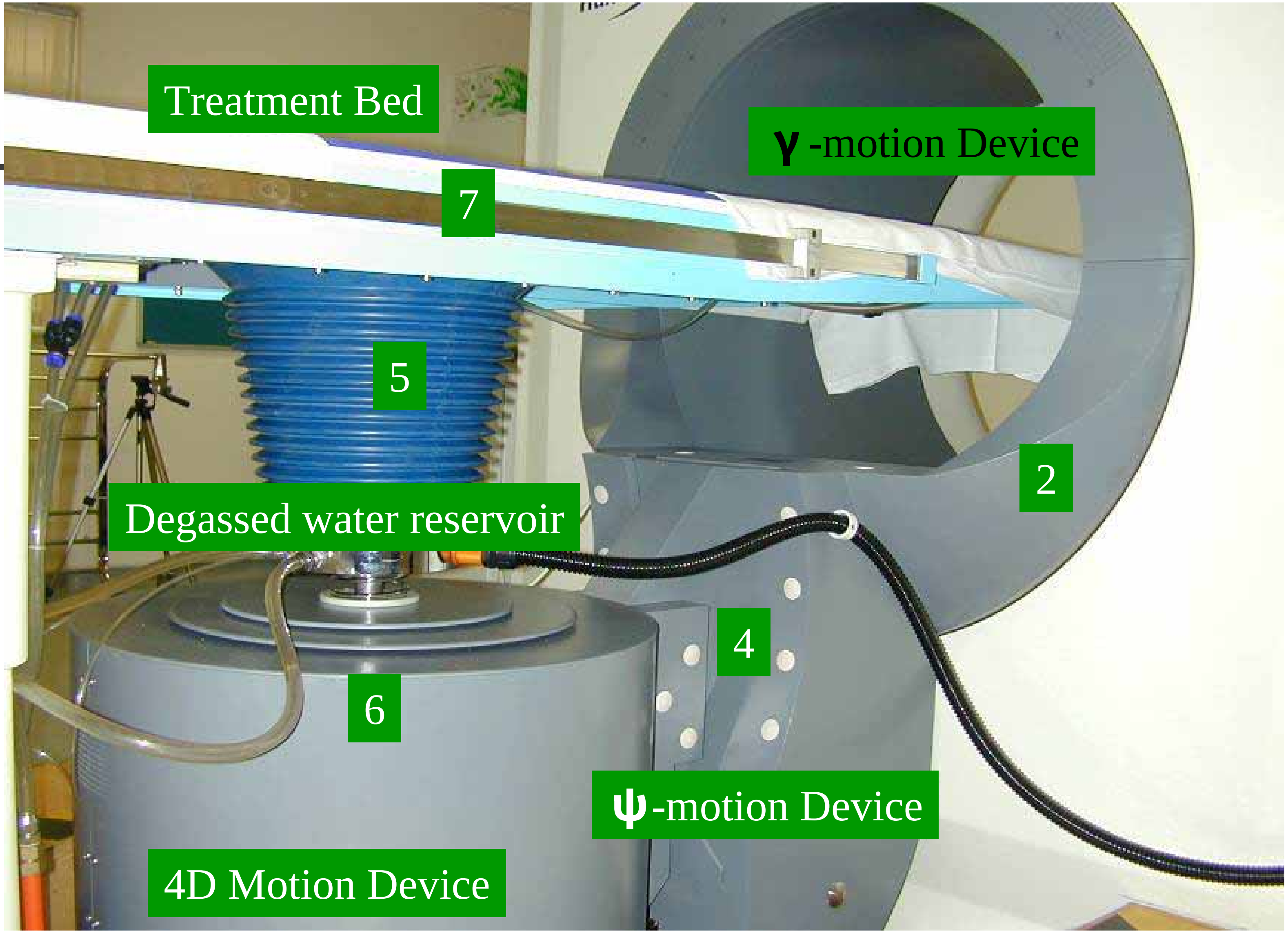
K L TAN & ASSOCIATES

Singapore

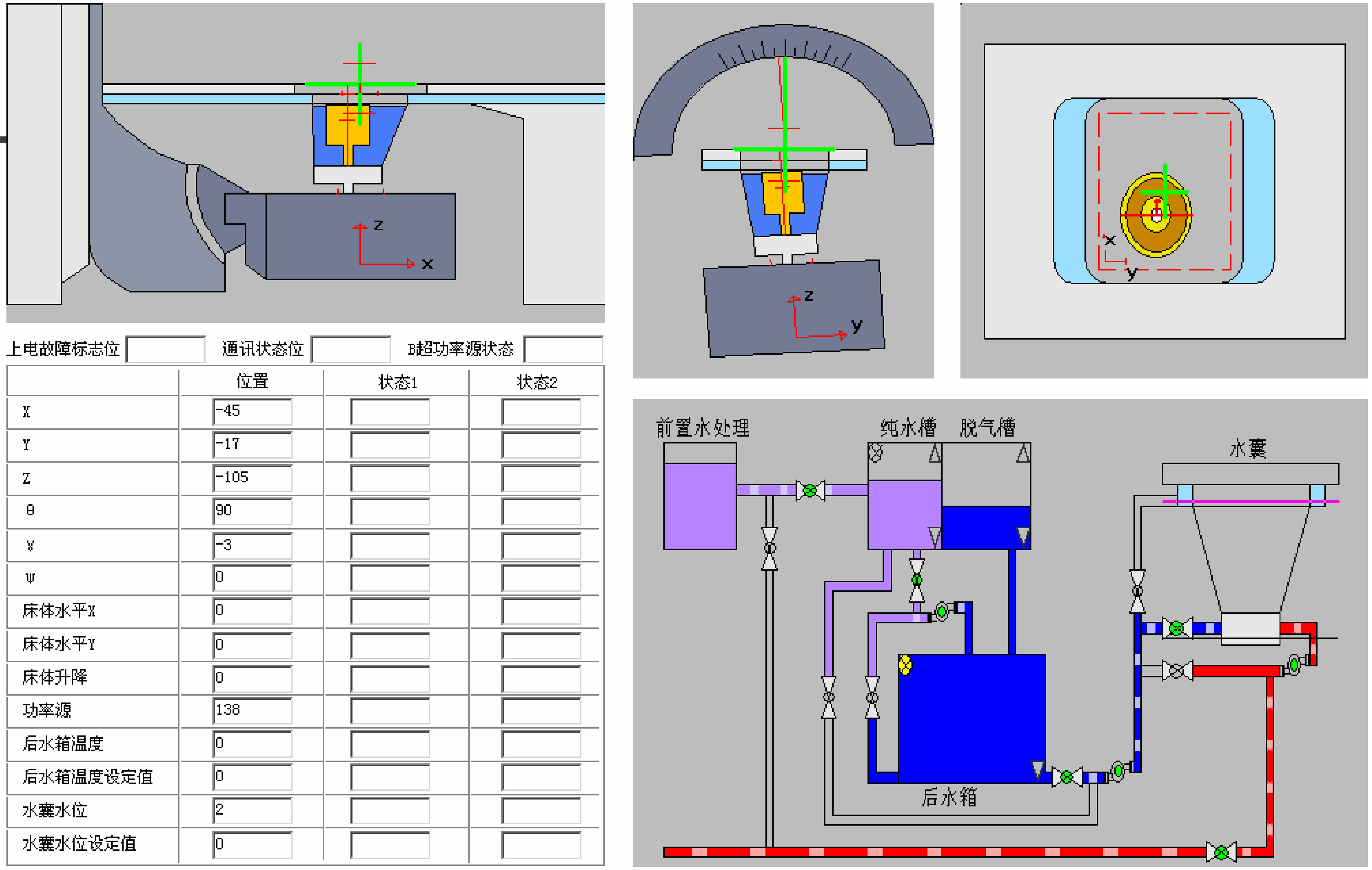
今 井 康 夫

Japan


γ -motion Device
Operator Console
2
3
Amplifier
1
7
4
6
ψ-motion Device
3+1 D Motion Device
Treatment Bed


Treatment Bed
γ -motion Device
7
5
2
Degassed water reservoir
4
6
ψ-motion Device
4D Motion Device

Integrated Treatment Transducer (diagnostic US probe and HIFU transducer) in degassed water reservoir



上电故障标志位
通讯状态位
B超功率源状态

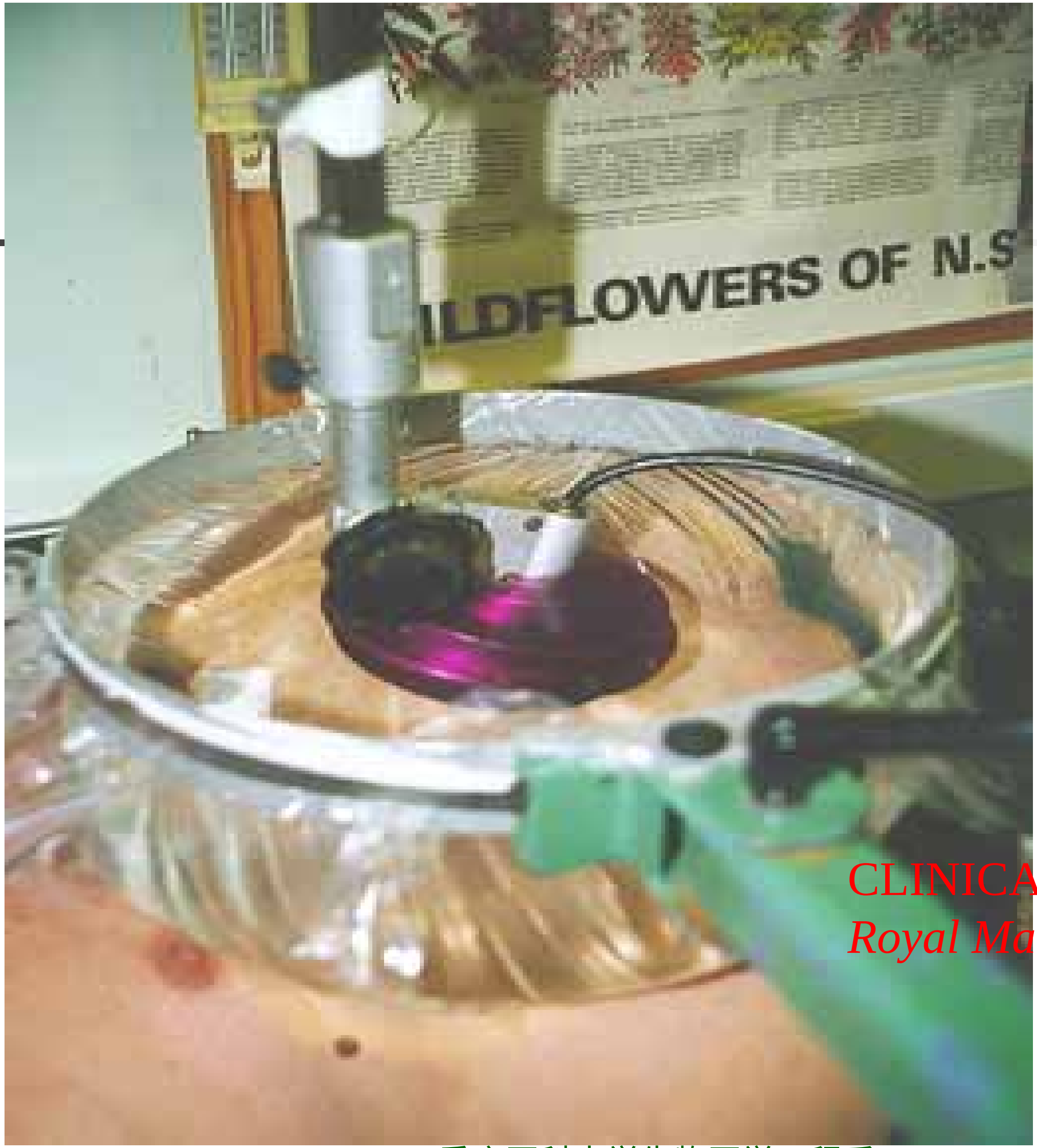
	位置	状态1	状态2
X	-45		
Y	-17		
Z	-105		
θ	90		
γ	-3		
ψ	0		
床体水平X	0		
床体水平Y	0		
床体升降	0		
功率源	138		
后水箱温度	0		
后水箱温度设定值	0		
水囊水位	2		
水囊水位设定值	0		

6-Dimension Motion system & Water Treatment System

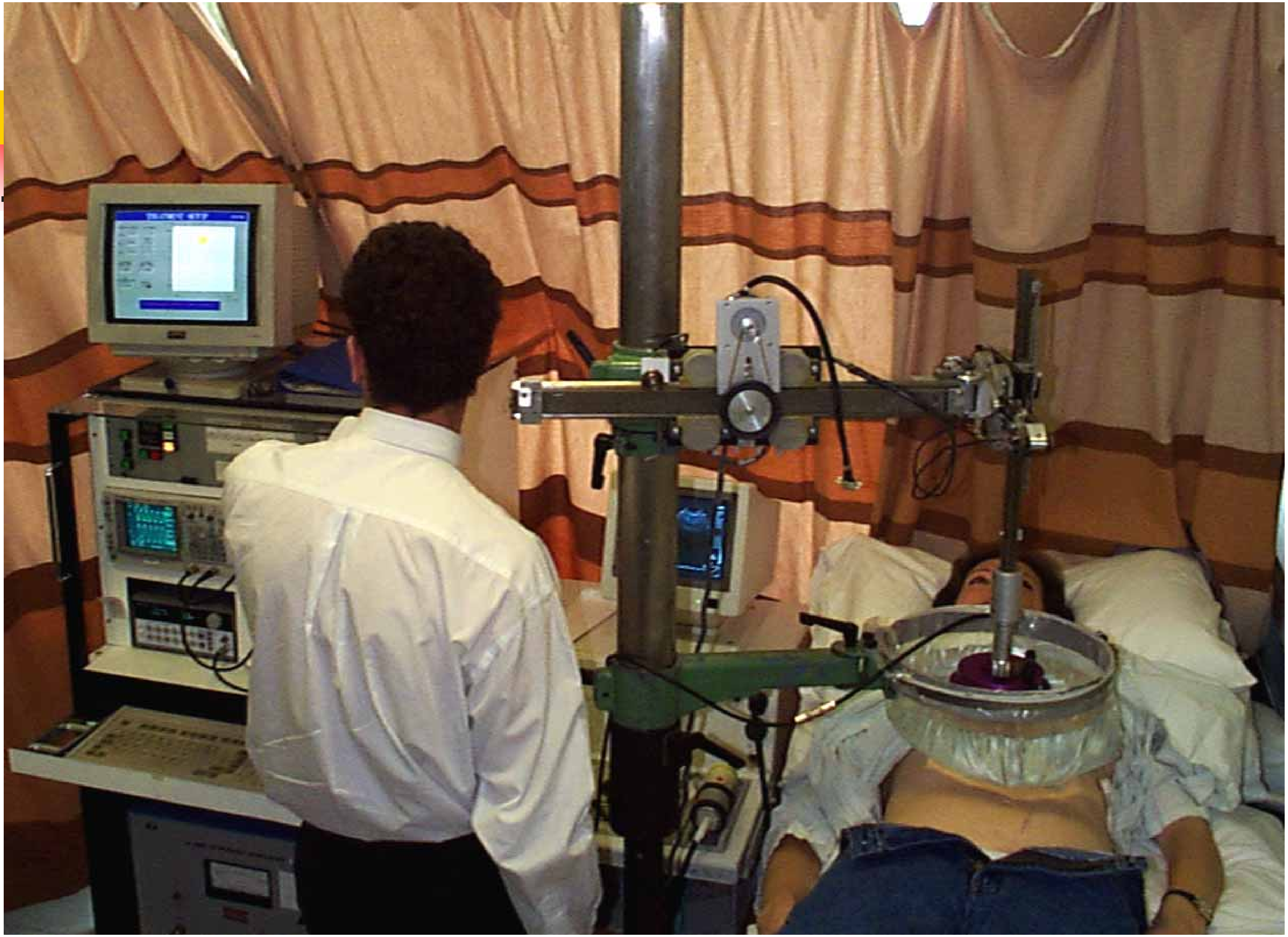
Haifu series products (Now and Future)

MR guided Focused Ultrasound Surgery

"FDA expedited review of the device because it offers significant advantages over existing treatments for uterine fibroids." – from FDA talk paper



CLINICAL PROTOTYPE
Royal Marsden Hospital, UK

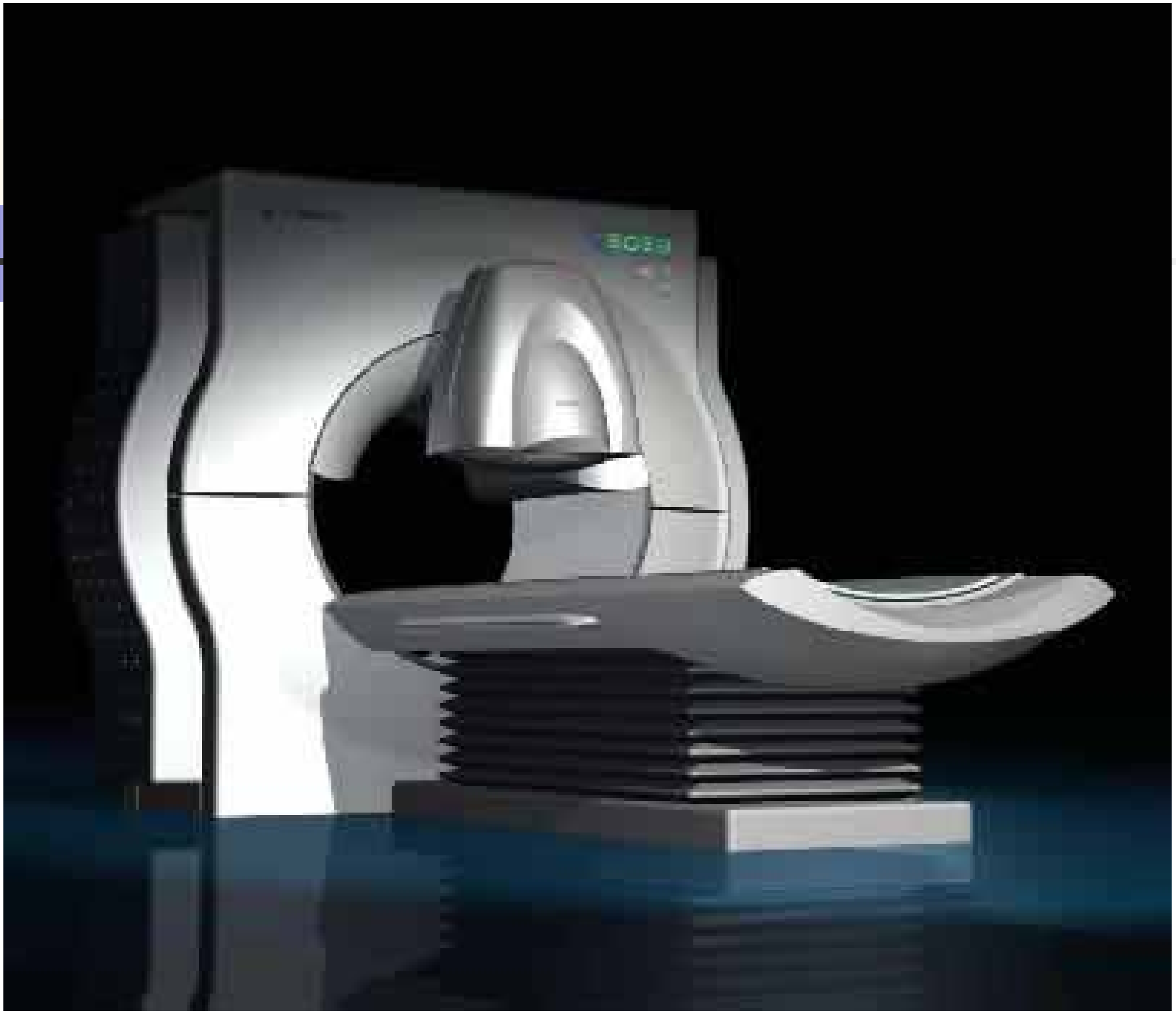



DKFZ / Siemens


Univ. Bordeaux

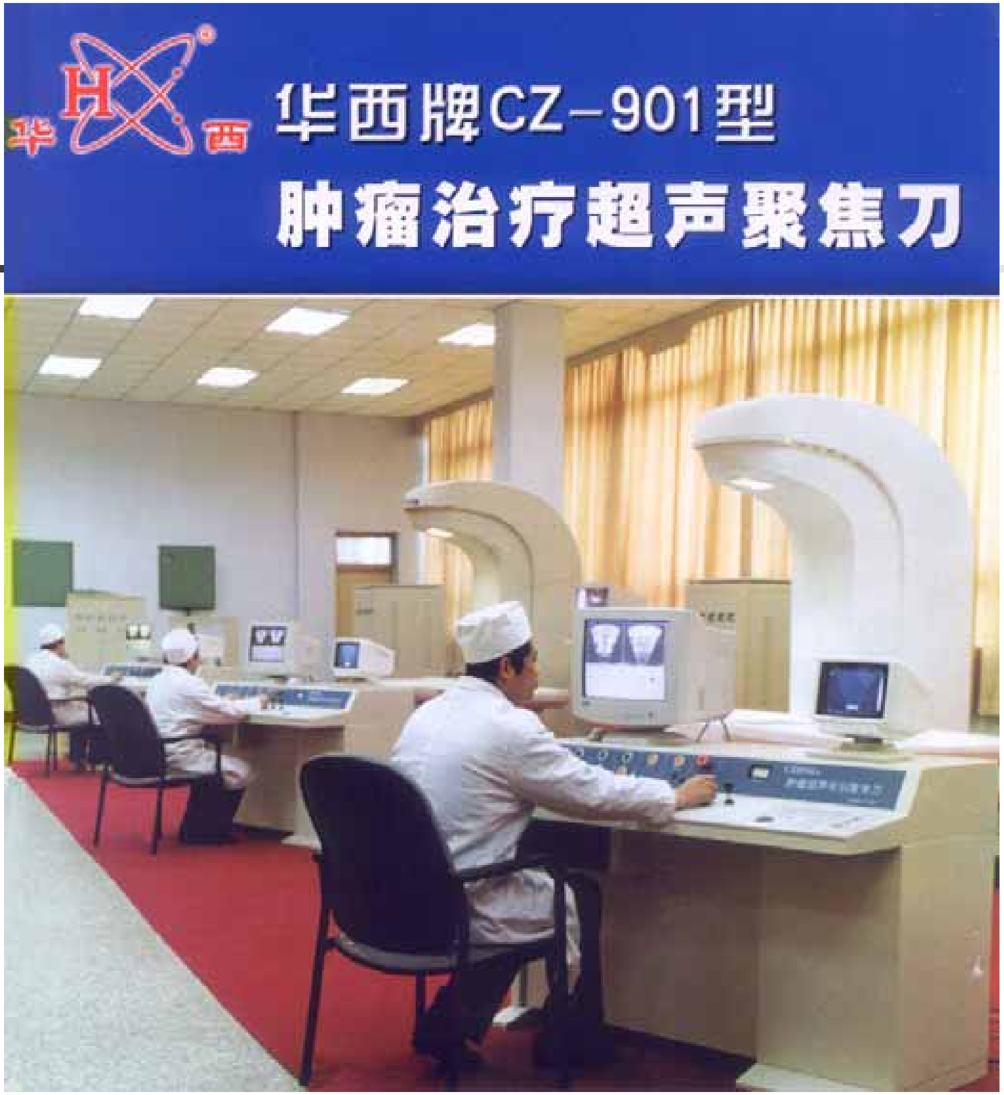
Beijing Yuande

FEP-BY01 High Energy Focused US Tumor Treatment Device reportedly has a operating frequency of 1 MHz under US monitoring. The US source emitting upward at present.



Shanghai Aishen

The HIFUNIT-9000 Aishen US Focused Tumor Ablation has reportedly 9 free-movement, 6 transducer emanating US downward. Each transducer has focal length of 8-14 cm and operating frequency of 1.0 MHz.



Sichuan Mianyang

Mianyang Sonic Electric Co., Ltd. developed CZ-901 Tumor Treatment US Knife. It is said to use in clinical application.

RDS HIFU Tumor Therapy Device developed by Redesheng Science & Technology Co., Ltd.

Shenzhen Xifukang

HIFU-2000立体定位高强聚焦超声肿瘤治疗系统由超声系统、治疗主机、电气控制系统、立体定位系统、HIFU-TPS治疗规划系统和水处理系统六部分组成。

HIFU-2000 Cubic Localization

HIFU Tumor Treatment System.

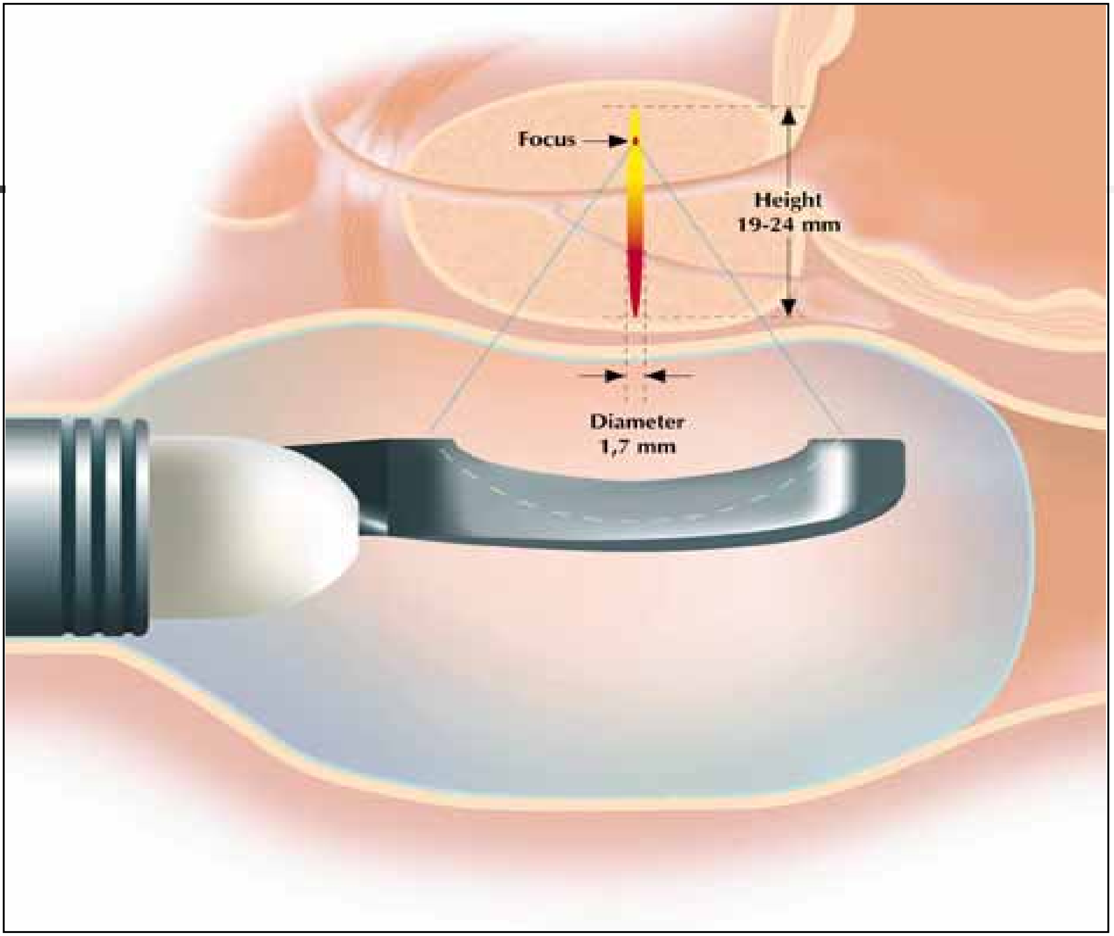
Operating Frequency: 0.8-5MHz

Peak Intensity: 1000W/cm^2

French EDAP-Technomed Inc. and Inserm

They have developed Ablatherm system for prostate cancer. It is reported that this machine has been used to treat more than 2000 patients since 1993.

Ablatherm system uses a 3 MHz transrectal transducer under US guidance.



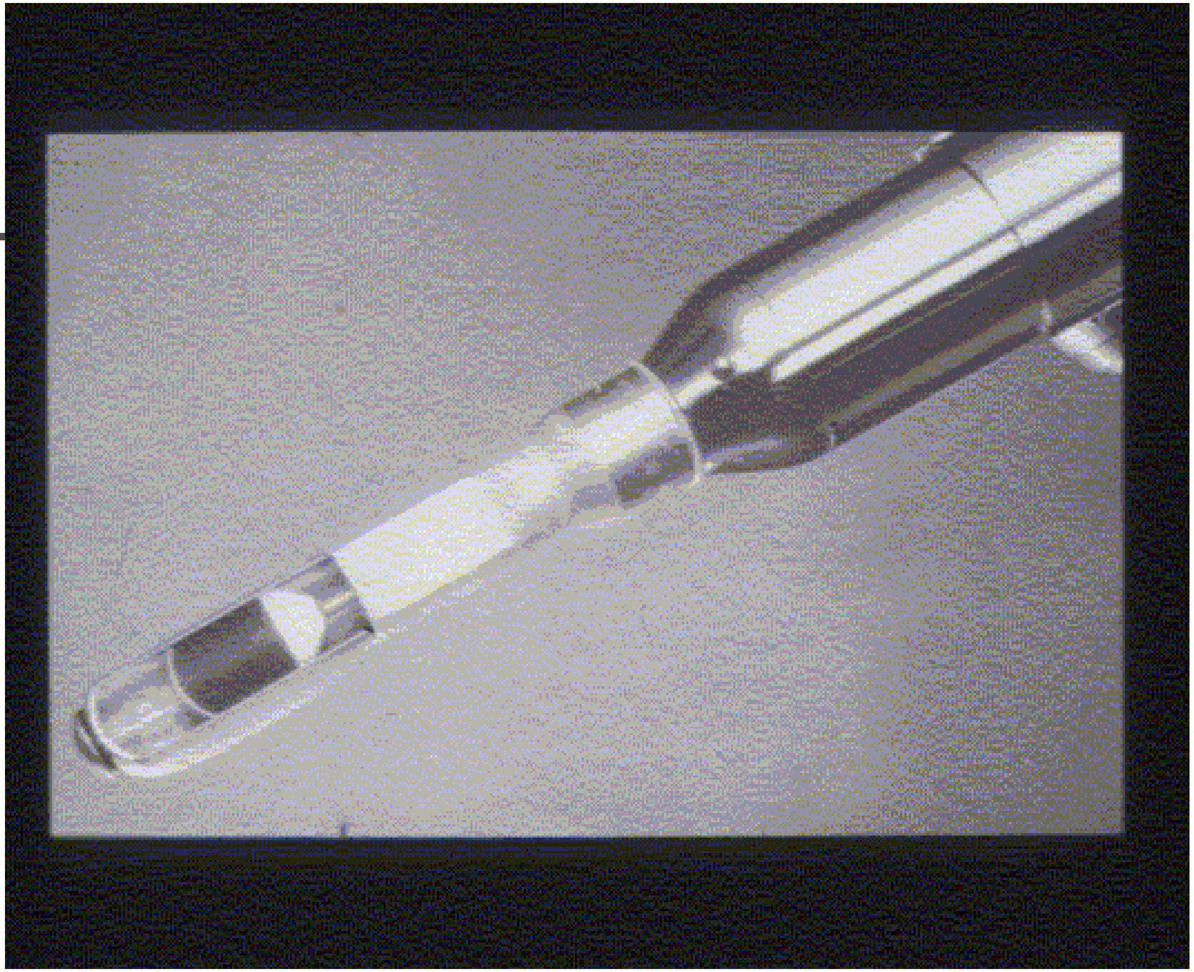
Ablatherm

Trans-rectal imaging & therapy probe

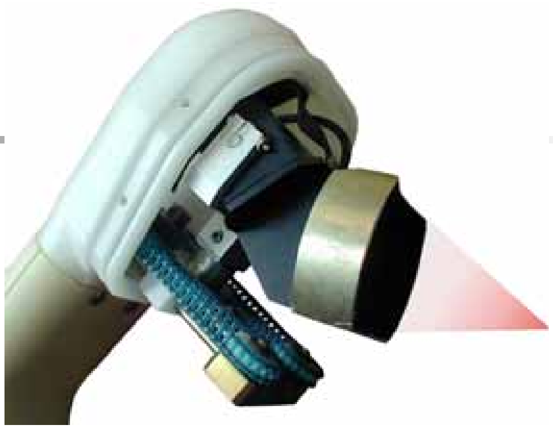
American Focus Surgery, Inc.

developed Sonablate® series devices for treating benign prostate hyperplasia (BPH). The system has gained phase Ⅲ clinical trial approval from FDA at present.

Sonablate®500, using diagnostic US for monitoring.



Trans-rectal imaging & therapy probe



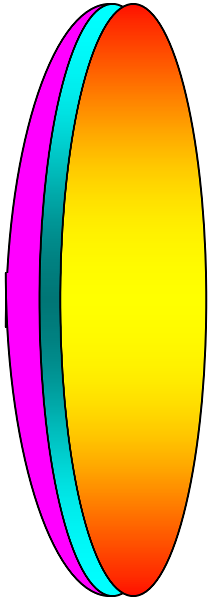
American Therus Co., undertakes the research and development of hemostasis using HIFU and has manufactured a device (Zhang 2001).

The Hemostasis Device produced by Therus Corporation. The transducer used has a diameter of 4.7 cm, focal length of 5.8 cm and operating frequency of 4.39MHz

Some reports (Lele, 1987 ;Ye,2002) pointed out that a HIFU surgical system should have the following characteristics:

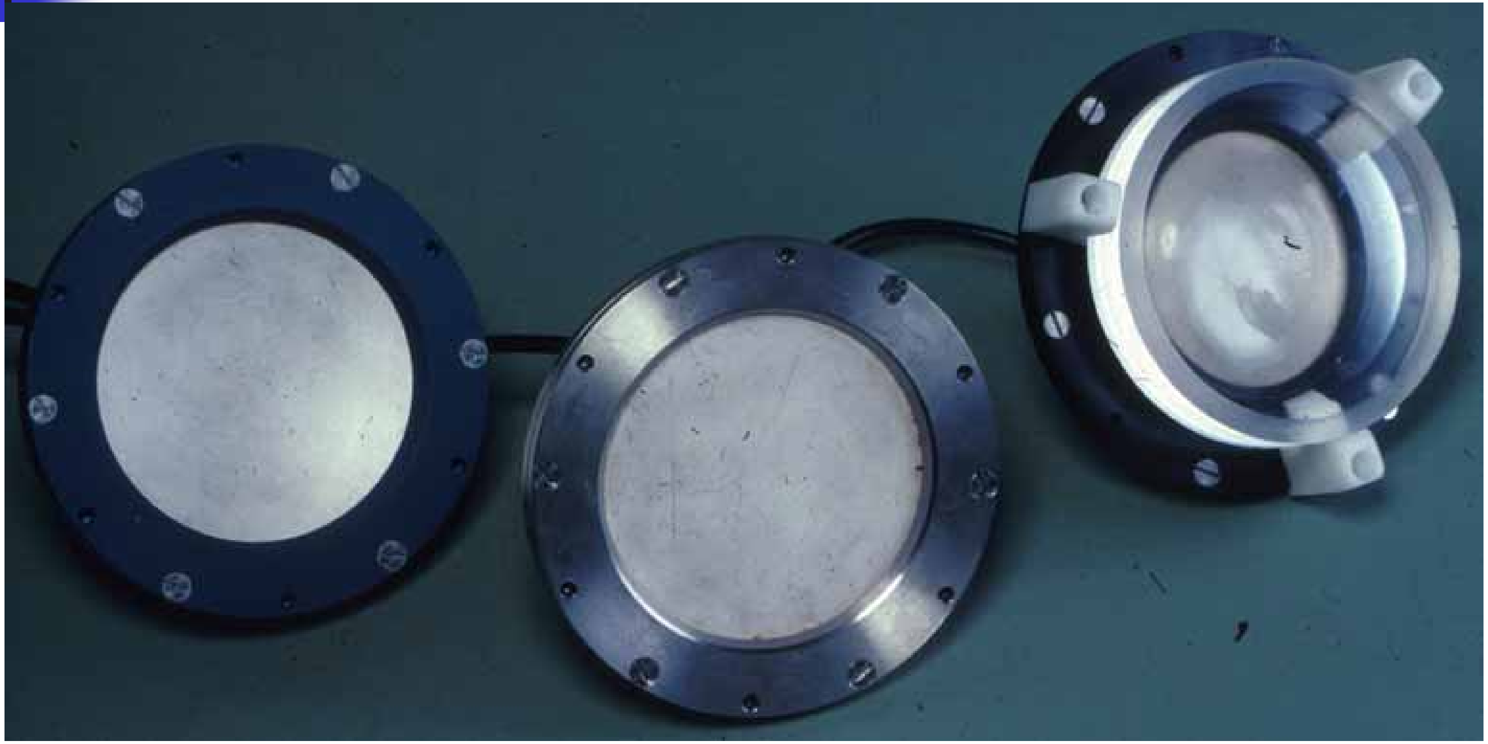
- The focusing or convergence of US beams, which induces evident coagulative necroses in tissue.
- Ultrasound beams of appropriate frequencies and high power heat only the region of interest, avoiding overheat at normal tissues in vicinity.
- Ultrasound energy possibly distributes on the whole target tissue, and a proper scanning speed and focused energy ensure the rapid elevation of temperature to what it is required.
- A convenient and adjustable scanning locus enables to heat target tissue of different shapes and to achieve ideal combination of coagulative necroses.
- Precisely selective destruction of target tissue and real-time monitoring to therapeutic effect are ensured.
- Due to the different tissue thickness of treating area, power compensation should be realized to protect those surrounding normal tissues sensitive to heat.

Therapeutic Ultrasound Transducer



Transducer geometries for therapy fields

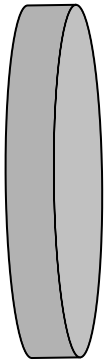
1. Plane
2. Plane + lens
3. Shaped – spherical bowl
   truncated bowl
4. Arrays
5. Multiple transducers

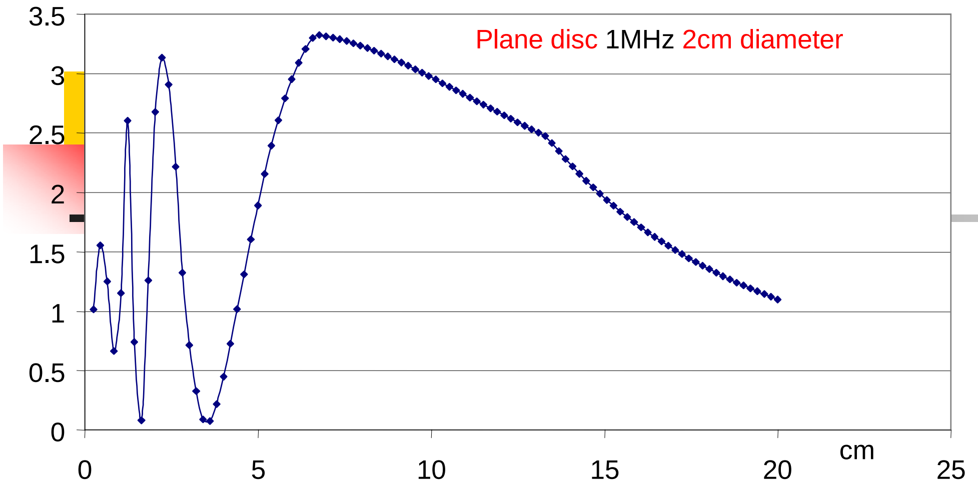


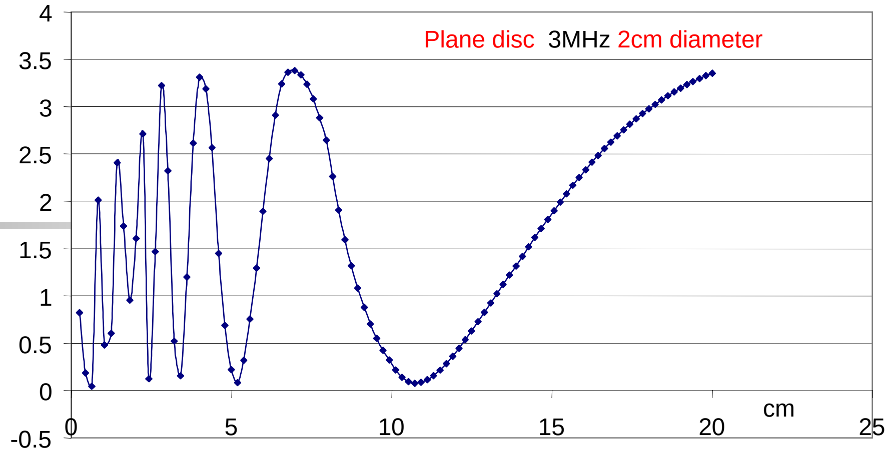
Bowl　　Plane　　Lens + plane

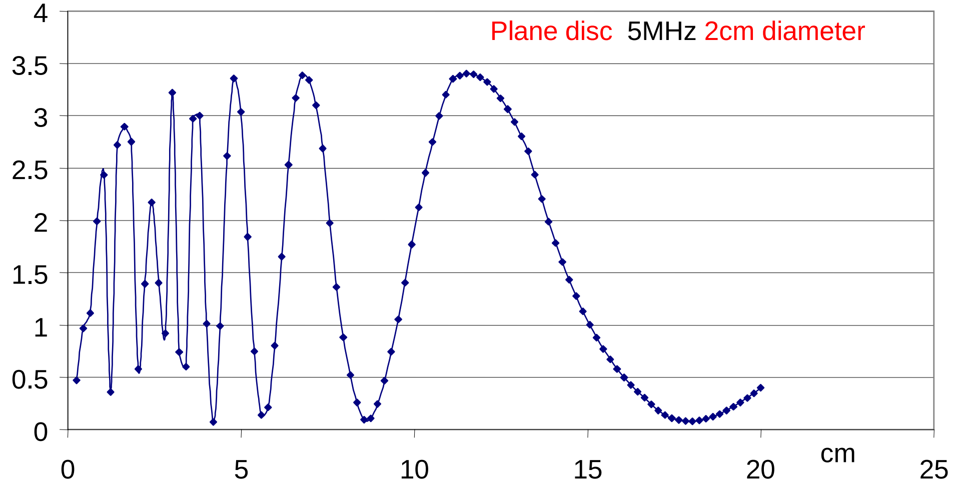
Plane Transducers

Flat disc, no focusing

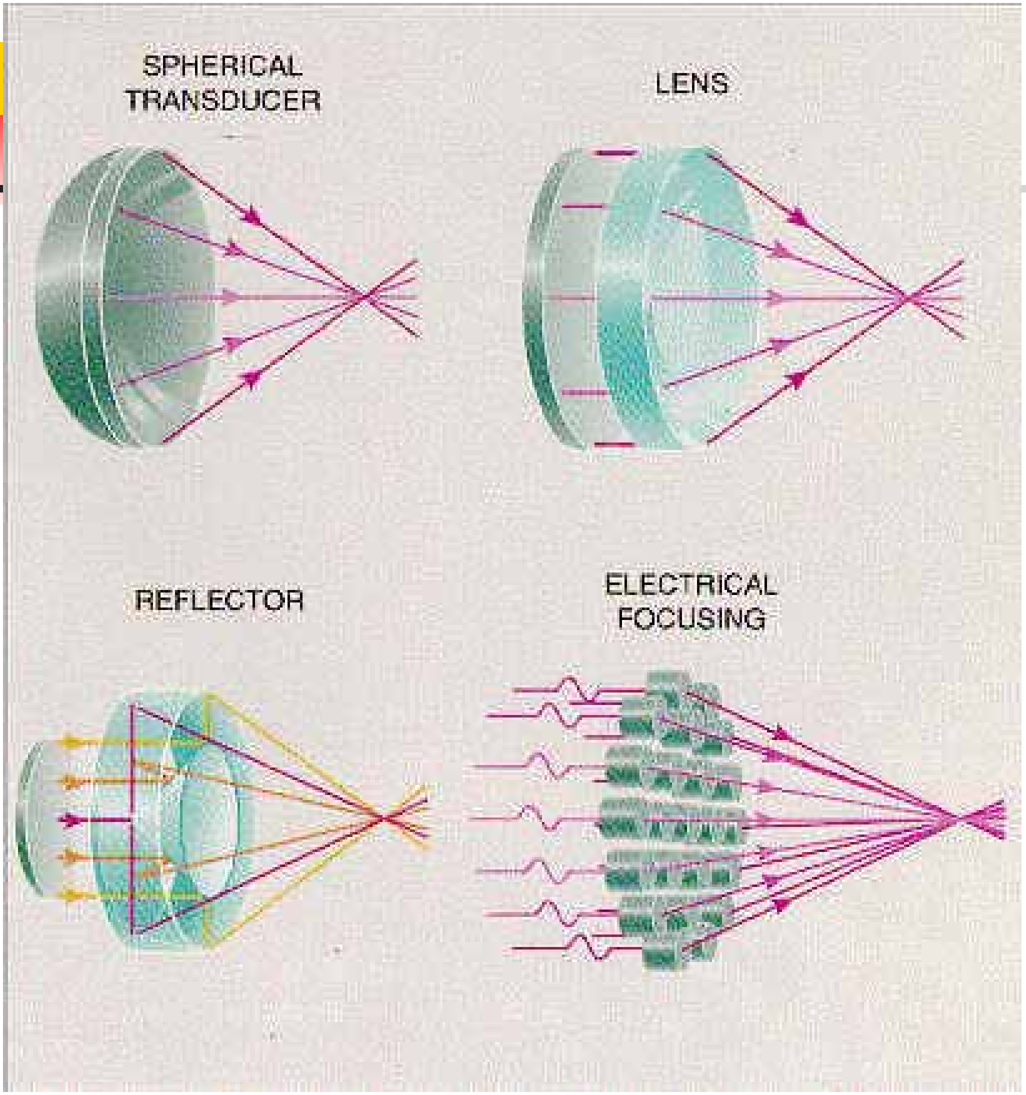






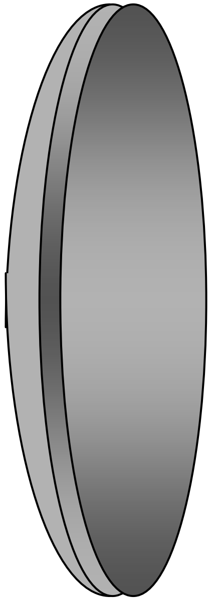


Near Field
extends
r^2/λ
from transducer face

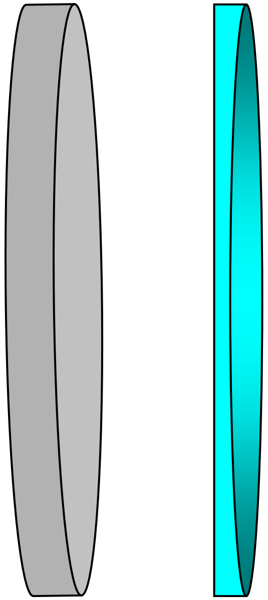


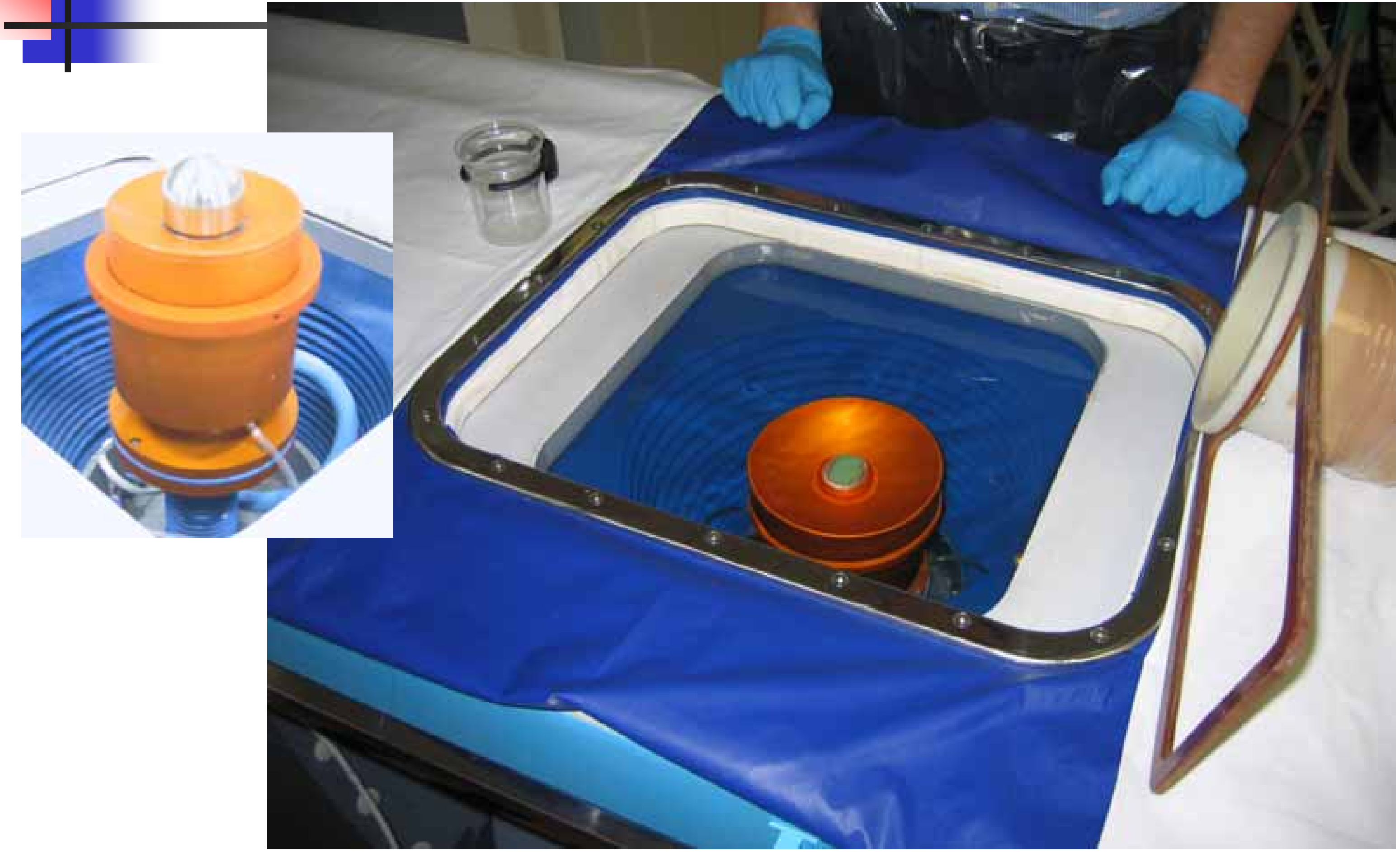
Ultrasound beams may be focused by curving the piezoelectric plate or by interposing a lens or reflector between a flat plate and the target. A phased array of transducers is focused electronically.

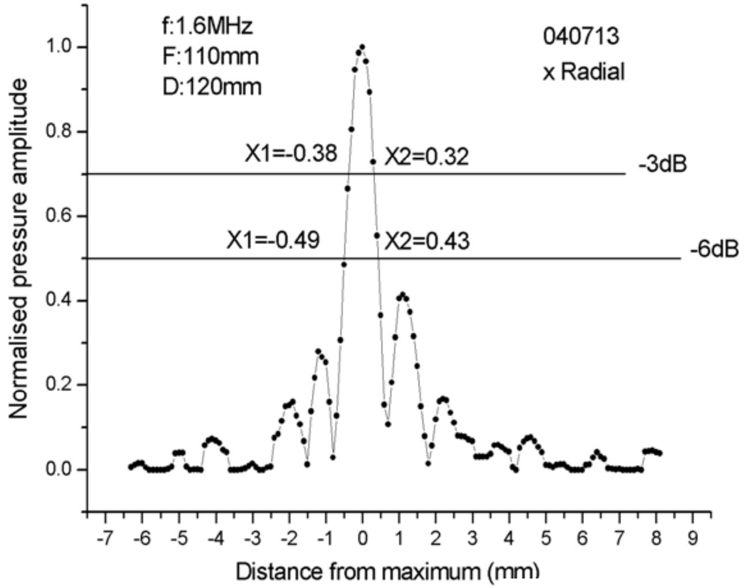
Single element Focused Bowls

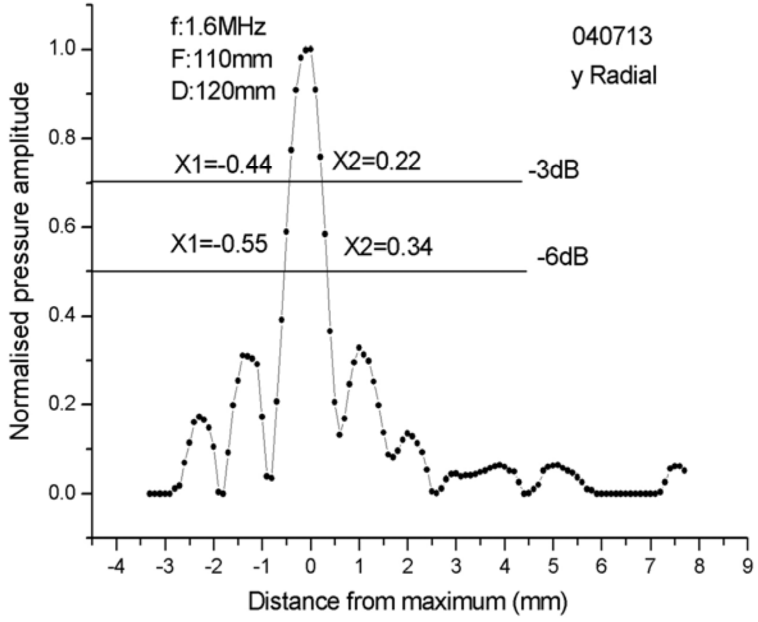


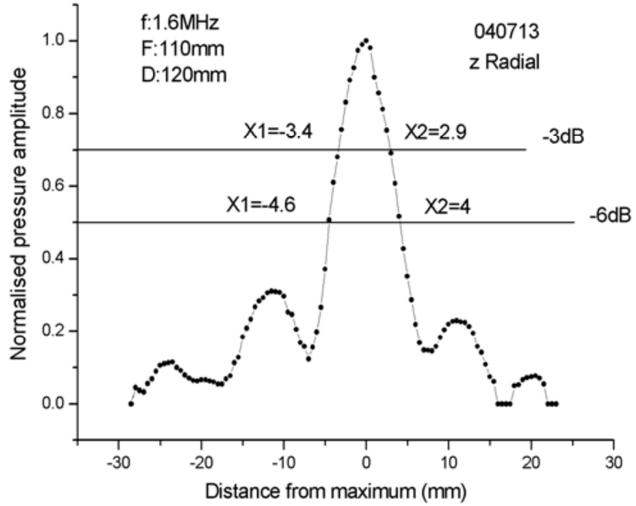
Plane transducers with a lens





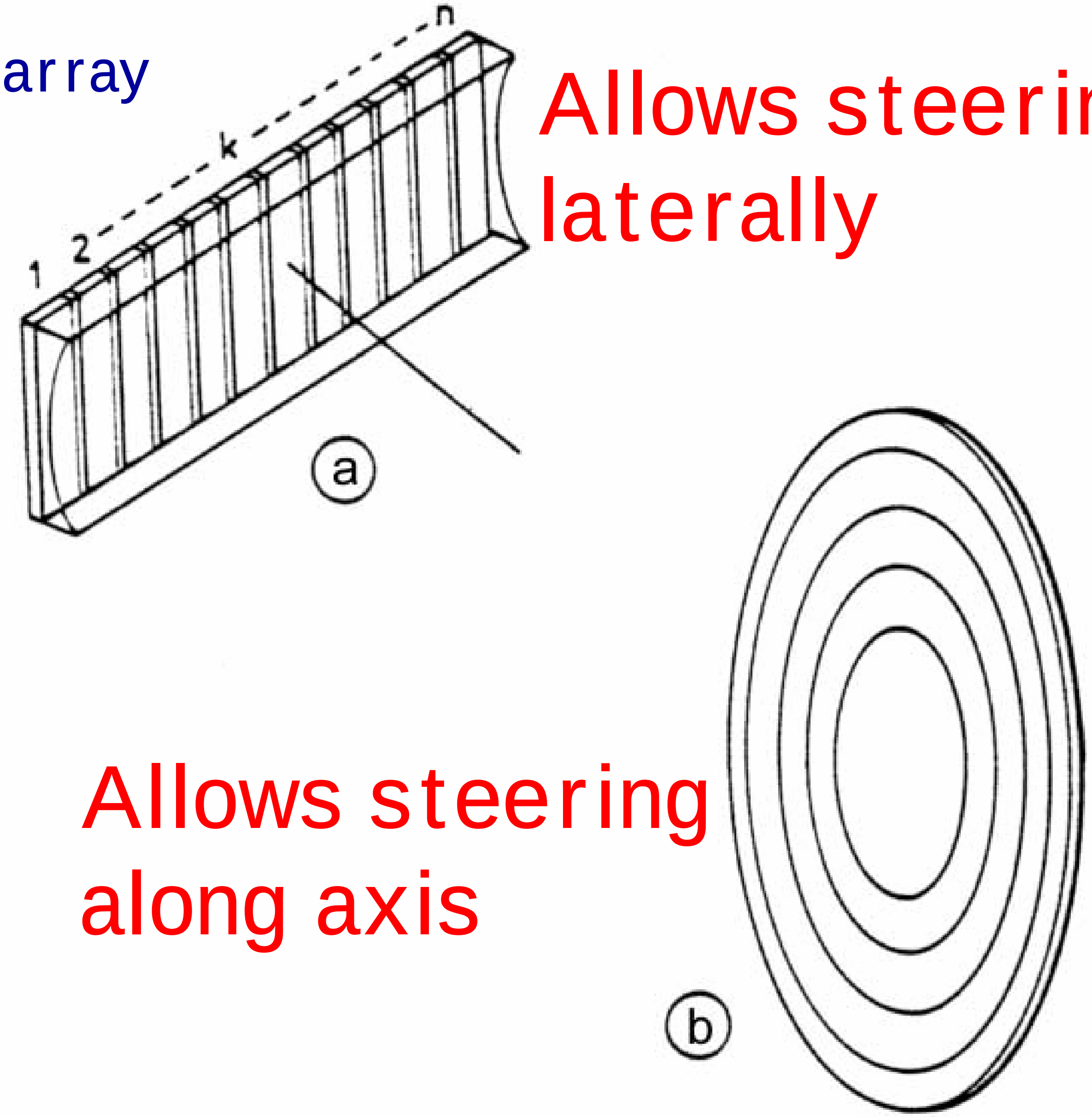

f:1.6MHz
F:110mm
D:120mm
040713
x Radial
X1=-0.38
X2=0.32
-3dB
X1=-0.49
X2=0.43
-6dB
Normalised pressure amplitude
0.0
0.2
0.4
0.6
0.8
1.0
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
Distance from maximum (mm)


f:1.6MHz
F:110mm
D:120mm
040713
y Radial
X1=-0.44
X2=0.22
-3dB
X1=-0.55
X2=0.34
-6dB
Normalised pressure amplitude
0.0
0.2
0.4
0.6
0.8
1.0
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
Distance from maximum (mm)


f:1.6MHz
F:110mm
D:120mm
040713
z Radial
X1=-3.4
X2=2.9
-3dB
X1=-4.6
X2=4
-6dB
Normalised pressure amplitude
0.0
0.2
0.4
0.6
0.8
1.0
-30
-20
-10
0
10
20
30
Distance from maximum (mm)

Array Transducers

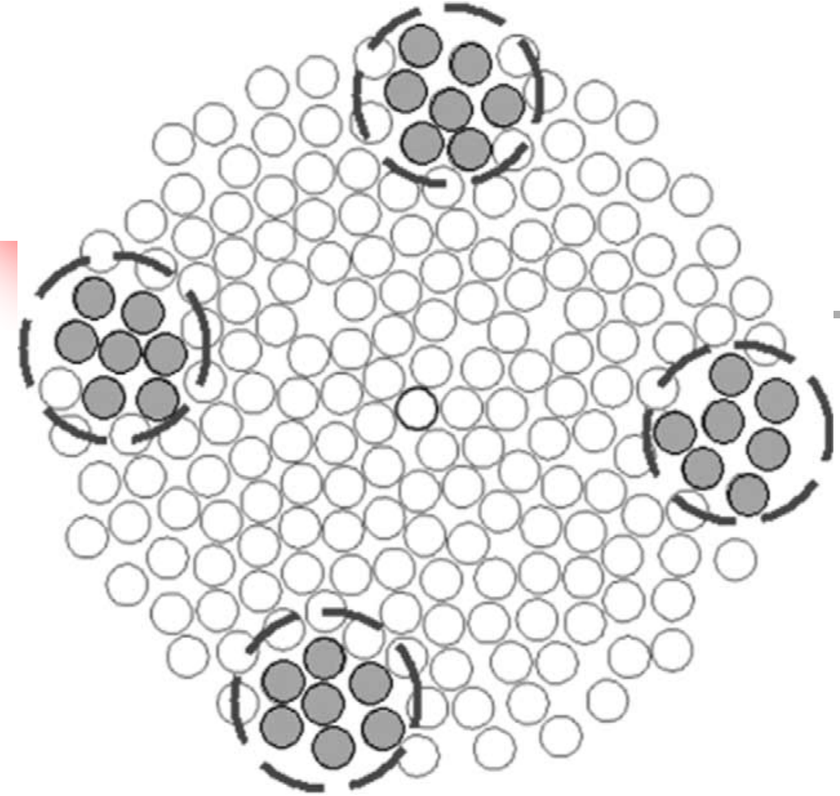
Linear array

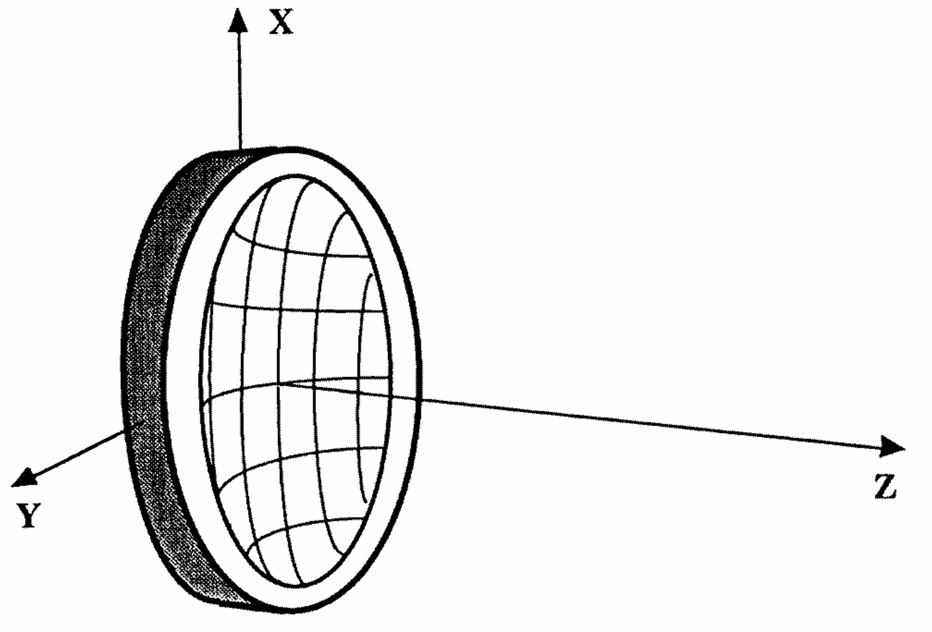


Allows steering laterally

Annular array

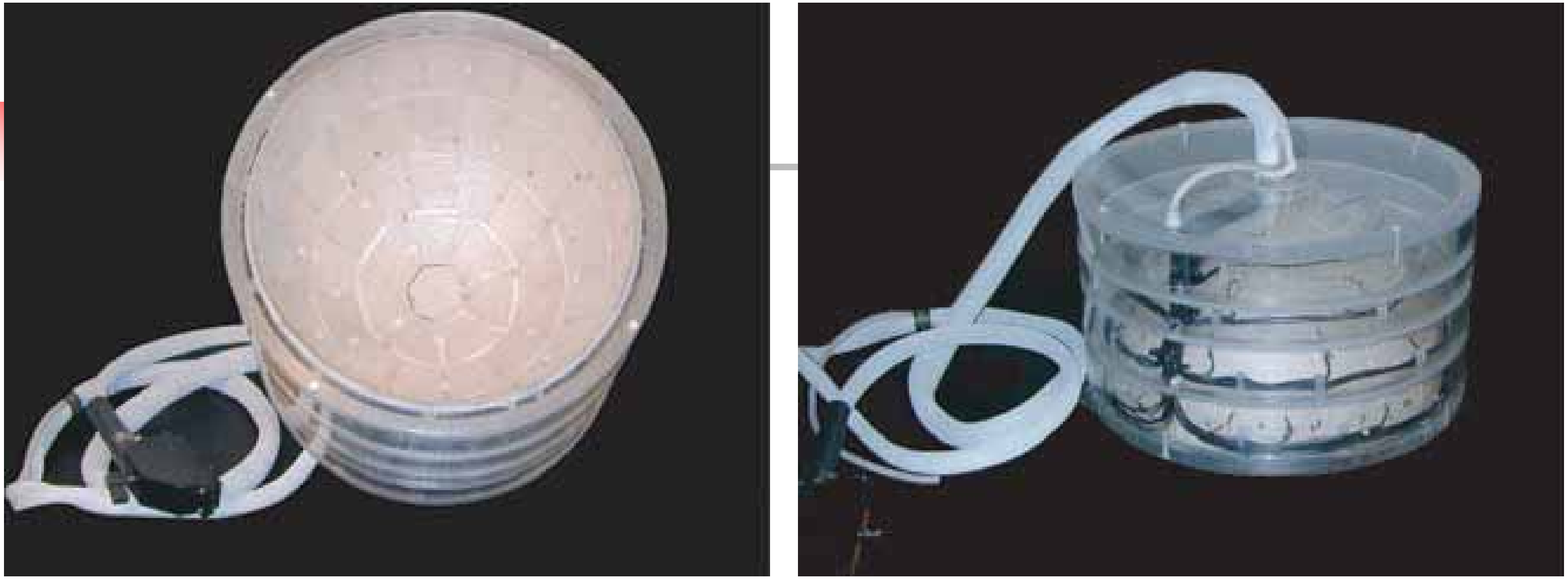
Allows steering along axis





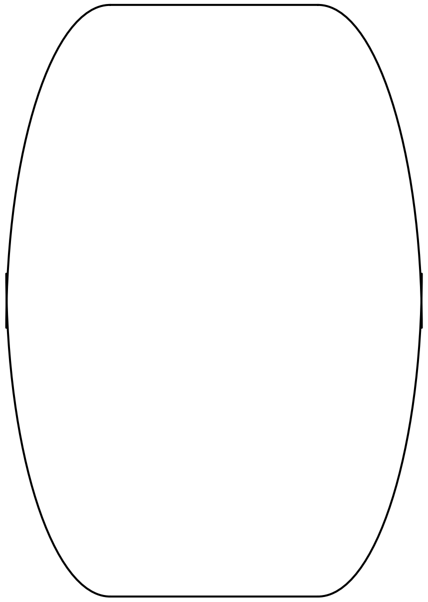
Array used by Paris group

Boston group's array



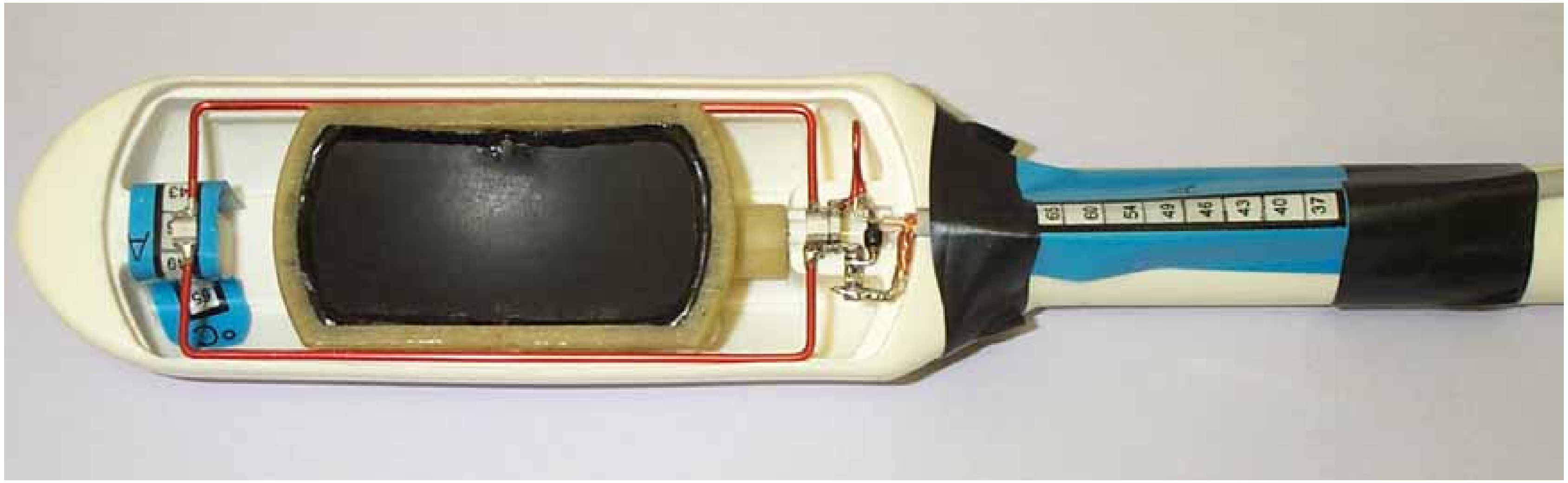
Hemispherical Bowls used for Brain HIFU by Boston group

Truncated bowls



Transrectal (Imasonic) transducer

- 1.7 MHz, 4.3 x 2.1 cm “diameter”, 4.0 cm focal length



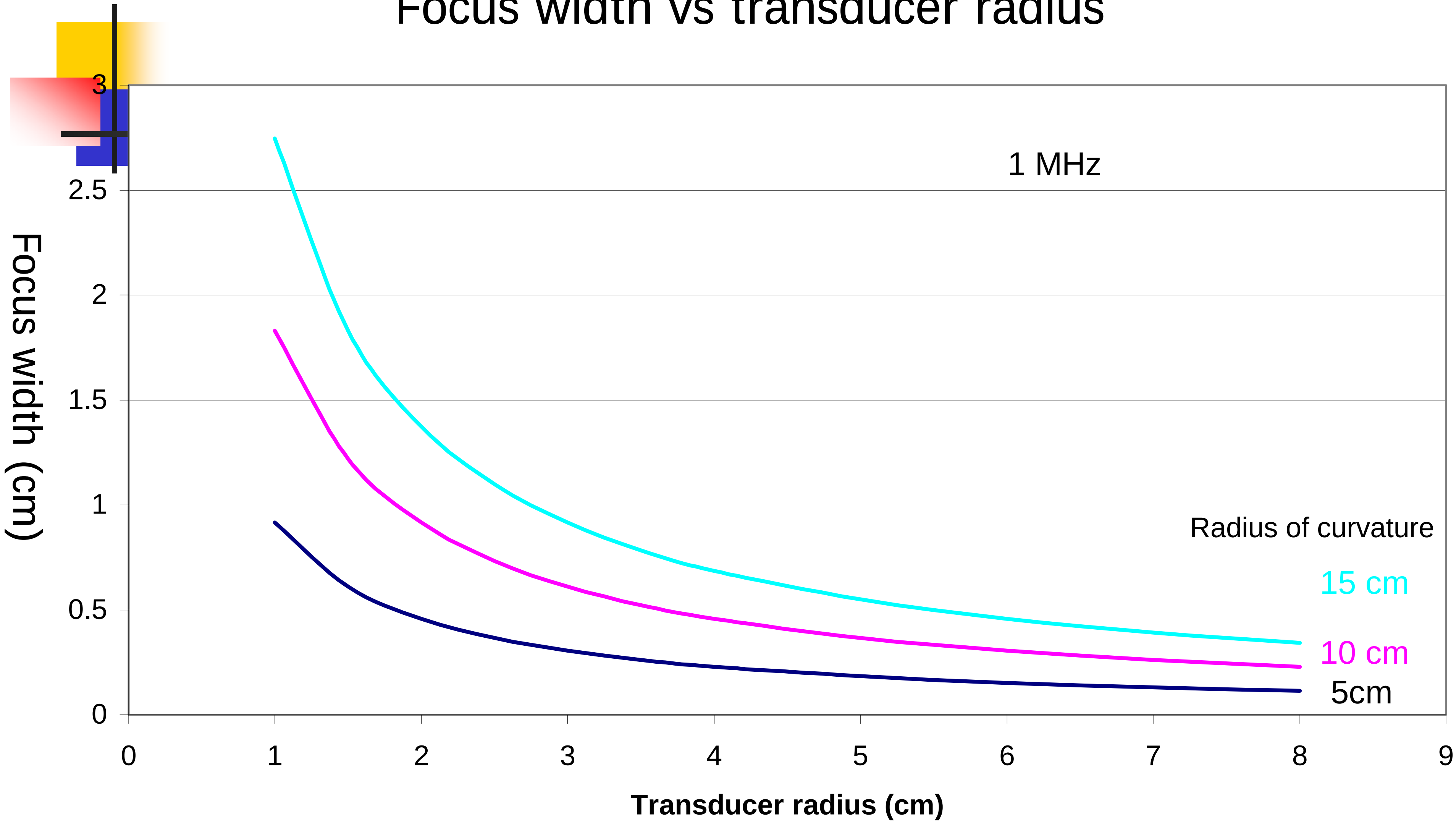
Focal (6dB) size: 3 x 2 mm dia. x 8 mm

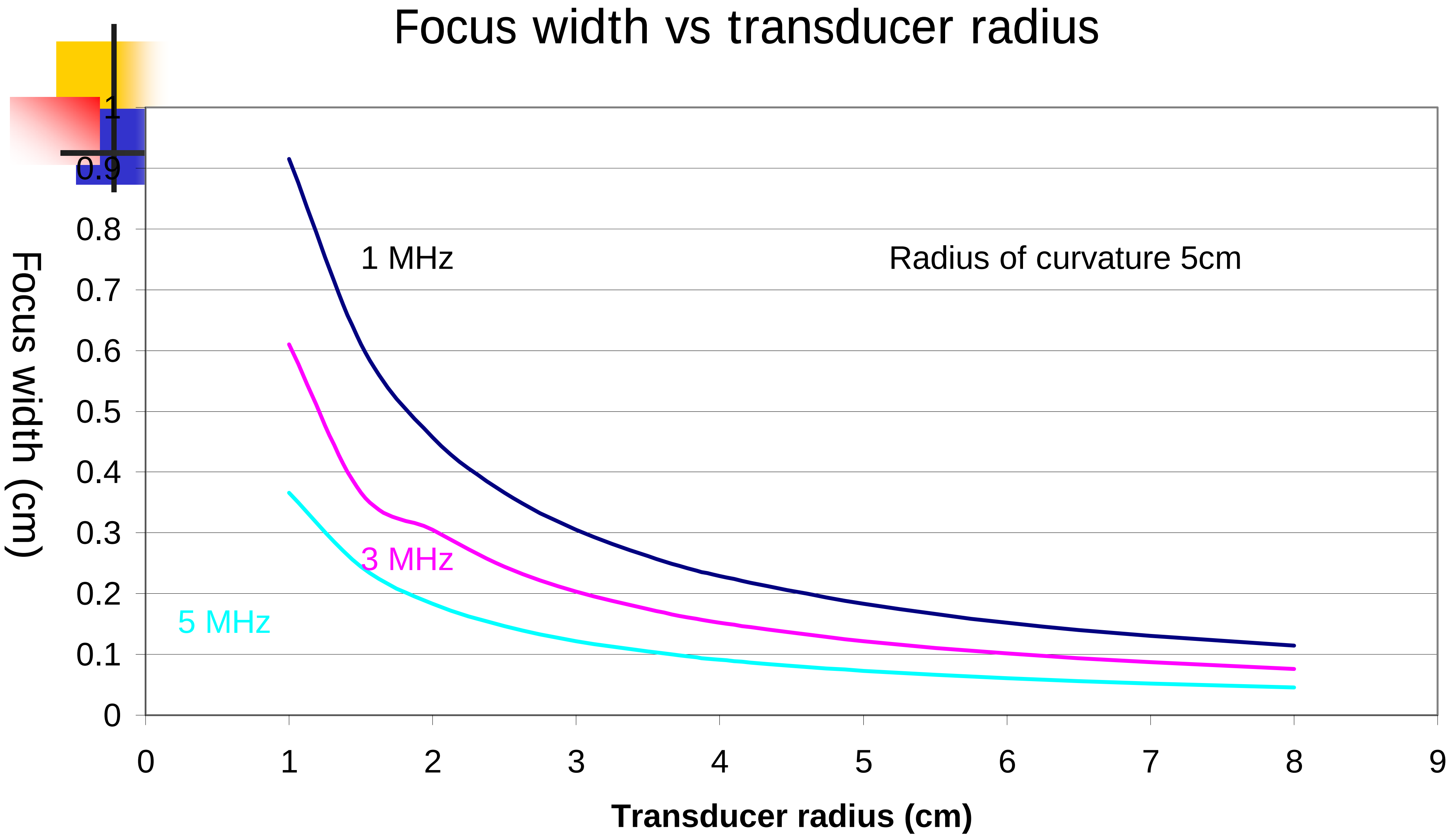
Design of a HIFU transducer

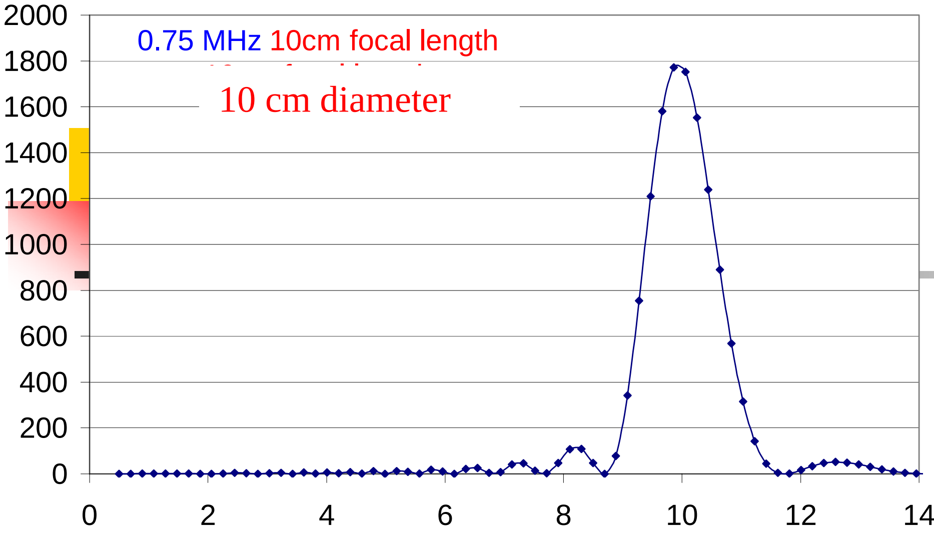
- To optimize :
  - Focal length (distance)
  - Focus length
  - Focus diameter (width)
    - F number
  - Side lobe level
  - Efficiency
  - Cooling

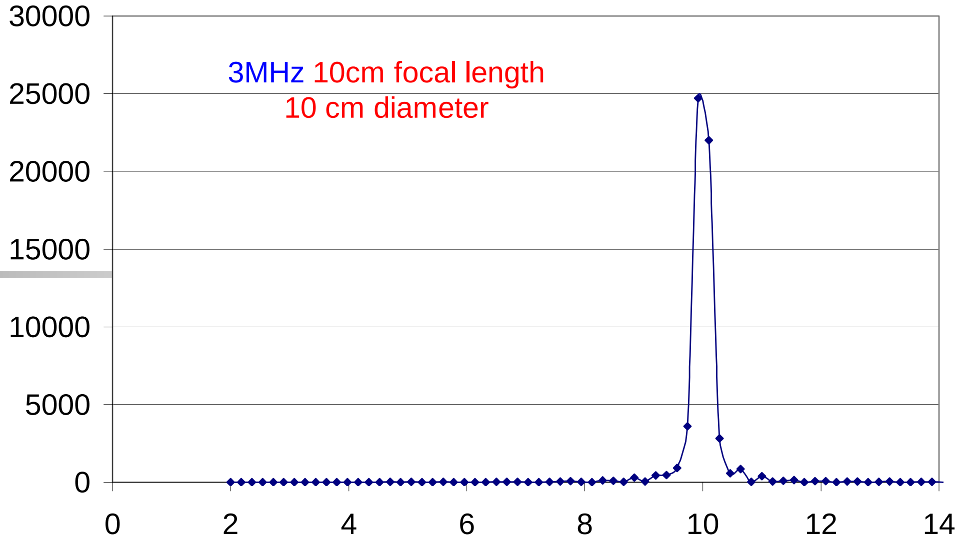
- By :
  - Frequency
  - Geometry
  - Type of material
  - Backing
  - Electrical matching
  - Acoustical matching

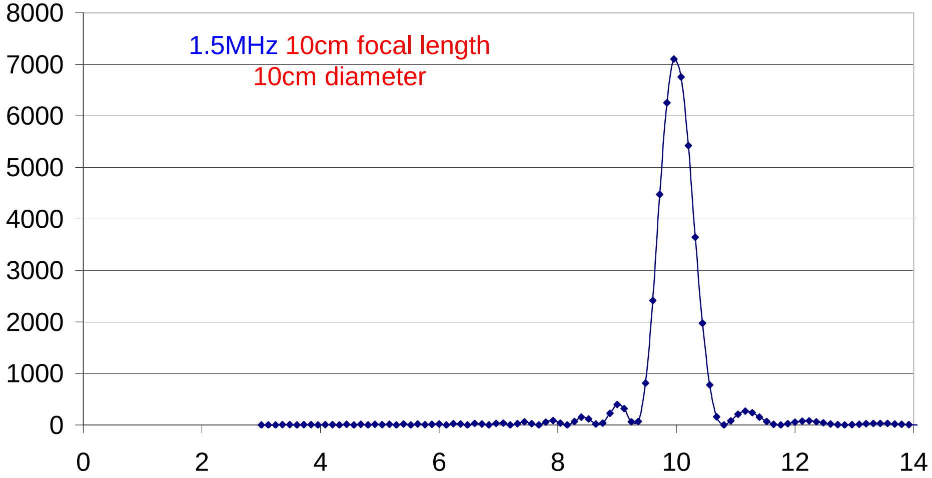
Focus width vs transducer radius




Focus width vs transducer radius
Focus width (cm)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1
2
3
4
5
6
7
8
9
Transducer radius (cm)
1 MHz
3 MHz
5 MHz
Radius of curvature 5cm

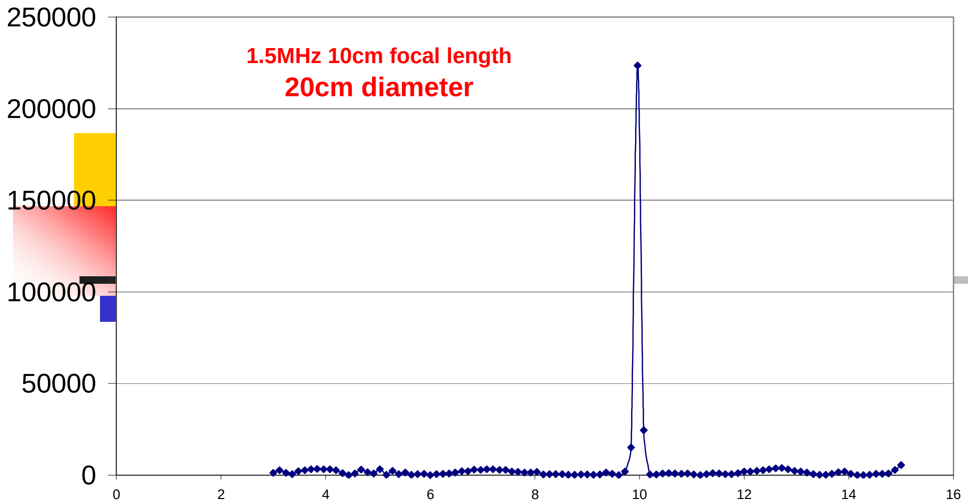


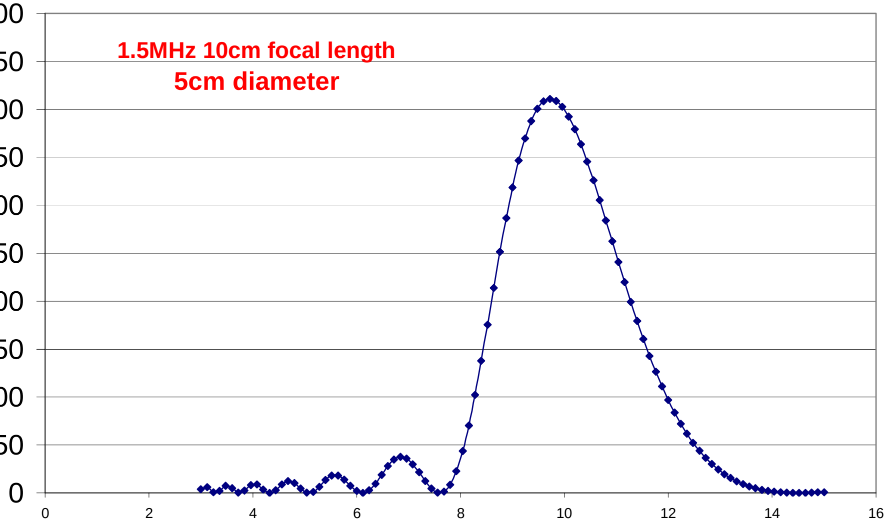


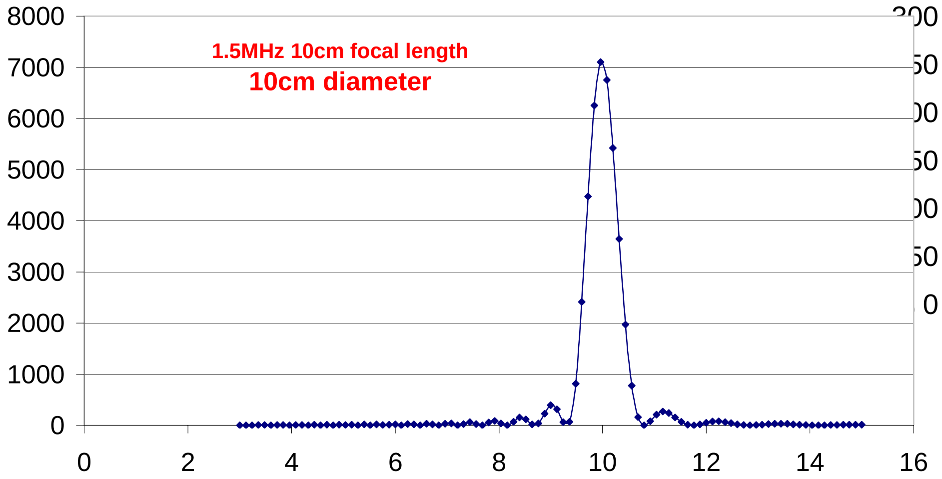


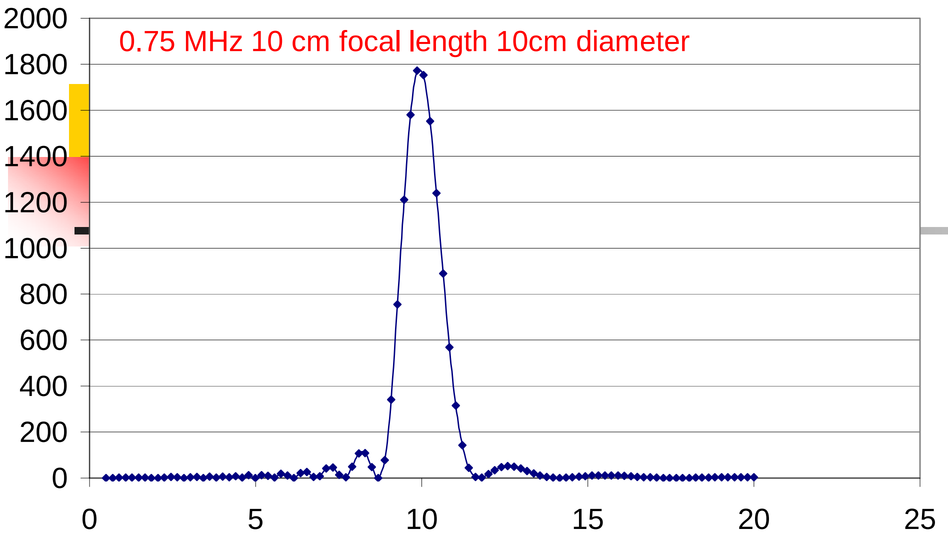
Effect of frequency

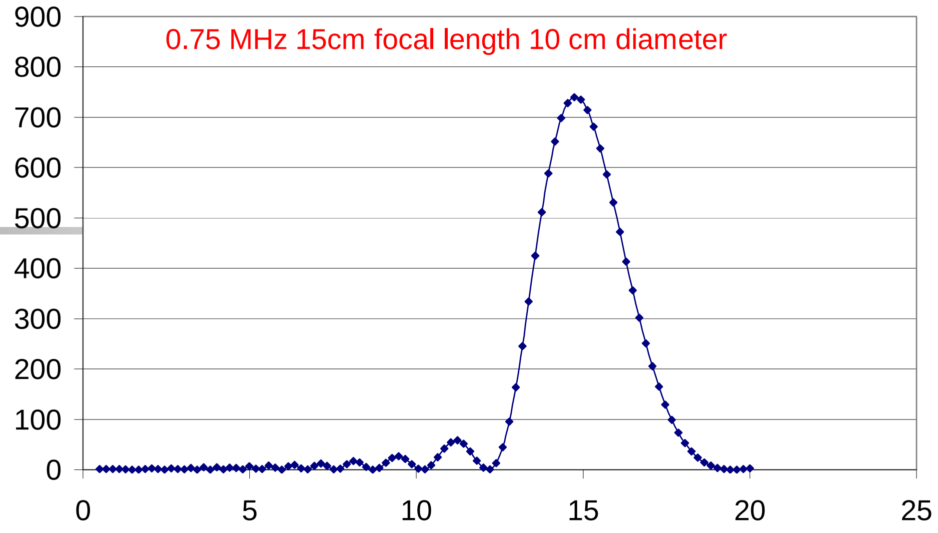
Effect of transducer diameter

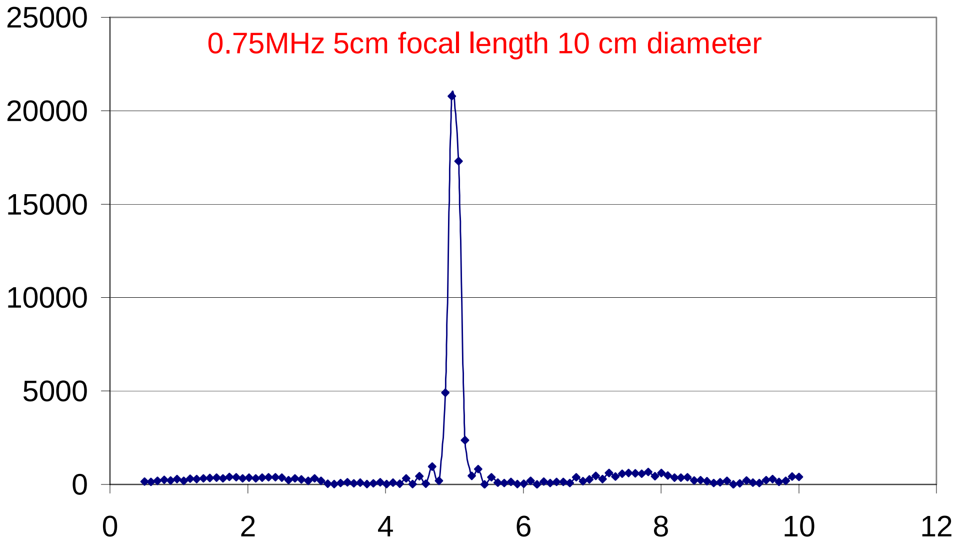




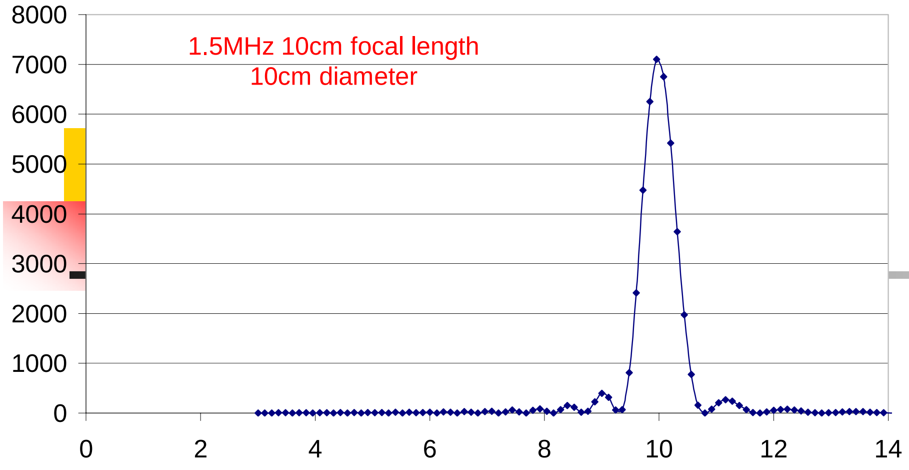


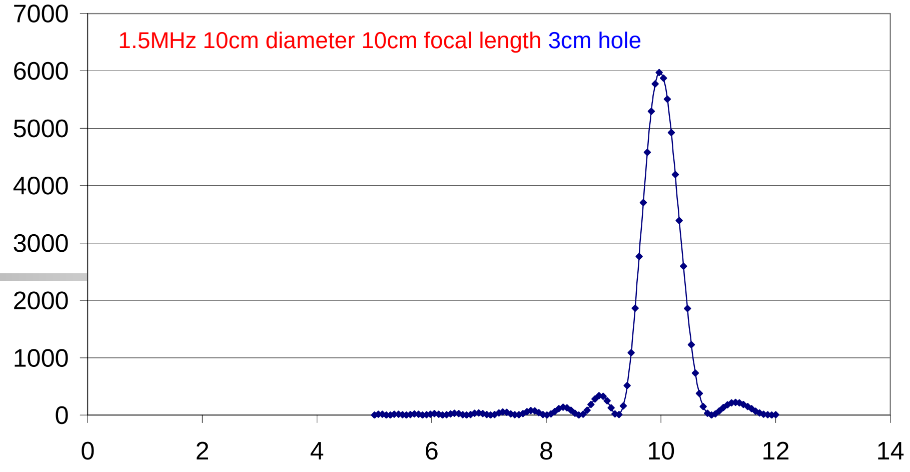


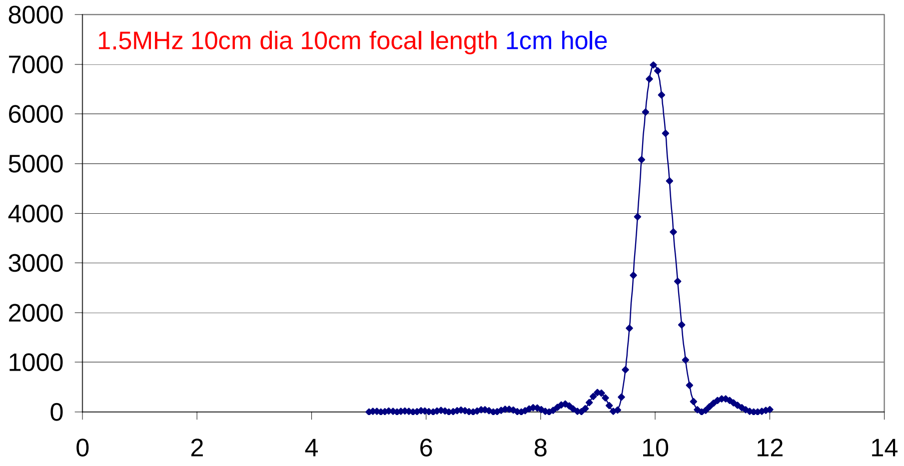


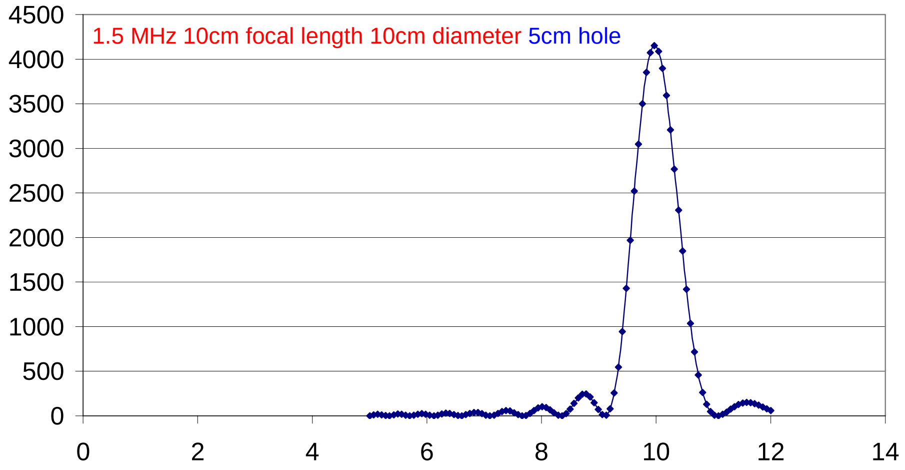


Change in focal length









Effect of central hole size

Impedance matching

Matching the electrical impedance
of the transducer
to its driving electronics
(*usually 50 Ω*)

Coupling Media

Coupling Media :requirements

1. Low reflectivity, high transmission
2. Ability to conform to skin surfaces
3. Ability to move the treatment head
   within it/in contact with it
4. Low gas content

Coupling Media :requirements

5. Controllable temperature
6. Ability to be contained
7. Plentiful and cheap
8. Sterility
9. Inert
10. Low attenuation coefficient

water is pretty good coupling media

Chap.8-2
The foundation of HIFU treatment cancer
——Biological effects of different tissues/tumor

Li Faqi
Department of Biomedical Engineering
Institute of Ultrasonic Engineering in Medicine
Chongqing Medical University

The investigate on HIFU biological effects is the base of HIFU treatment tumour.

Feasibility

Safety

Effectiveness

The physical mechanisms of HIFU biological effects

■Thermal □ Mechanical effect

-56^0C 1s

■ Cavitation

-Complex, and unpredictable

-Mechanical damage

-Tissue vibrate

-Stable cavitation and inertial cavitation

-Dependent on frequency, negative pressure amplitude and intensity

-May damage tissue

-May enhance heating

-May aid imaging

Approaches

- Objects

  Cell、Phantom、in vitro tissue 、in vivo animal、Bearing-tumour animal

- Characteristics of test system

  Acoustic field 、output （frequency、waveform、acoustic power）、focal length

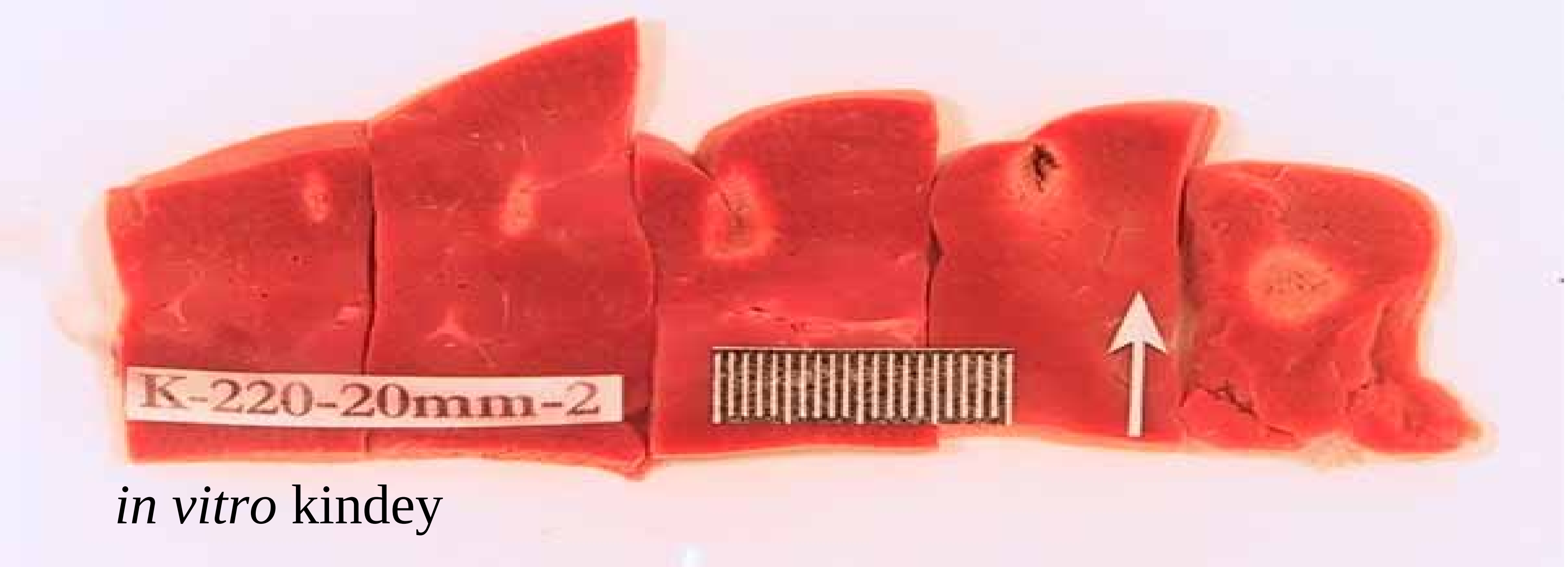
- Evaluating methods

  Macrography、histopathology、molecular biology、imaging

Biological effects of HIFU in *in vitro* tissue

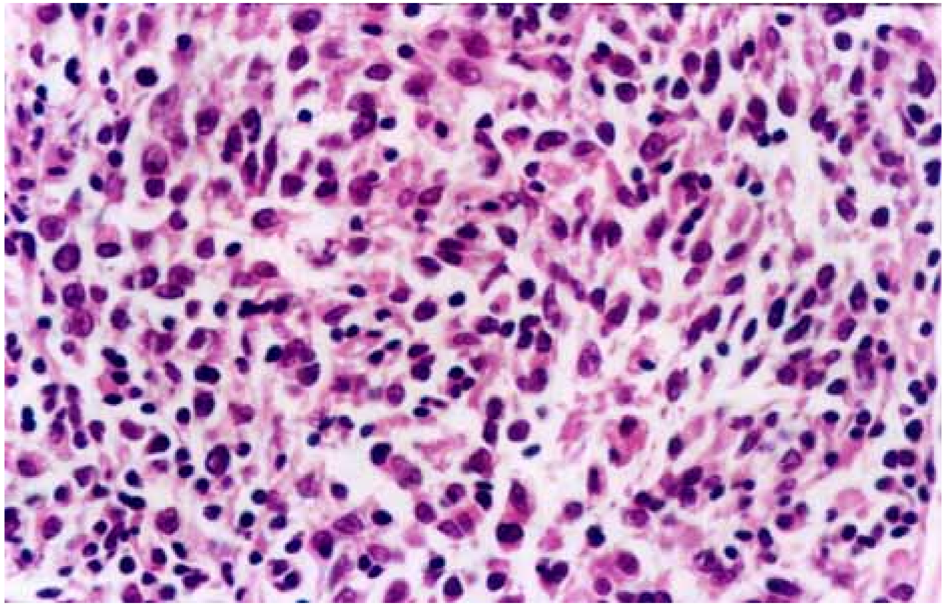
For a same acoustic power and at a same focal depth in tissue, BFR induced in ox liver with HIFU of different frequency and exposure time.

in vitro muscle



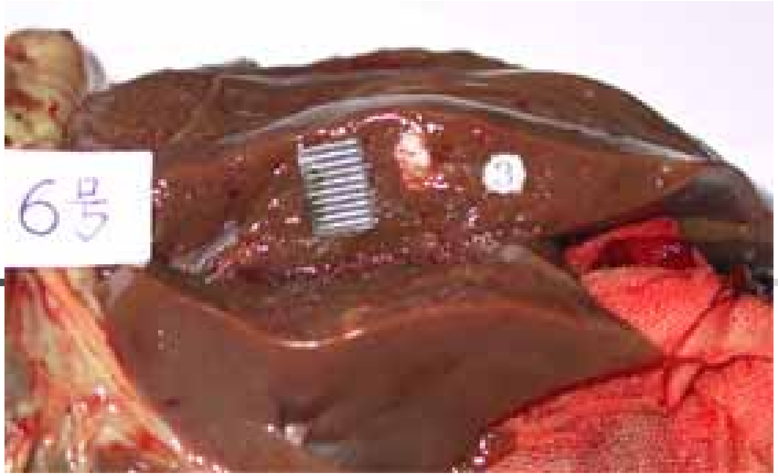
in vitro kindey

The human uterus sample

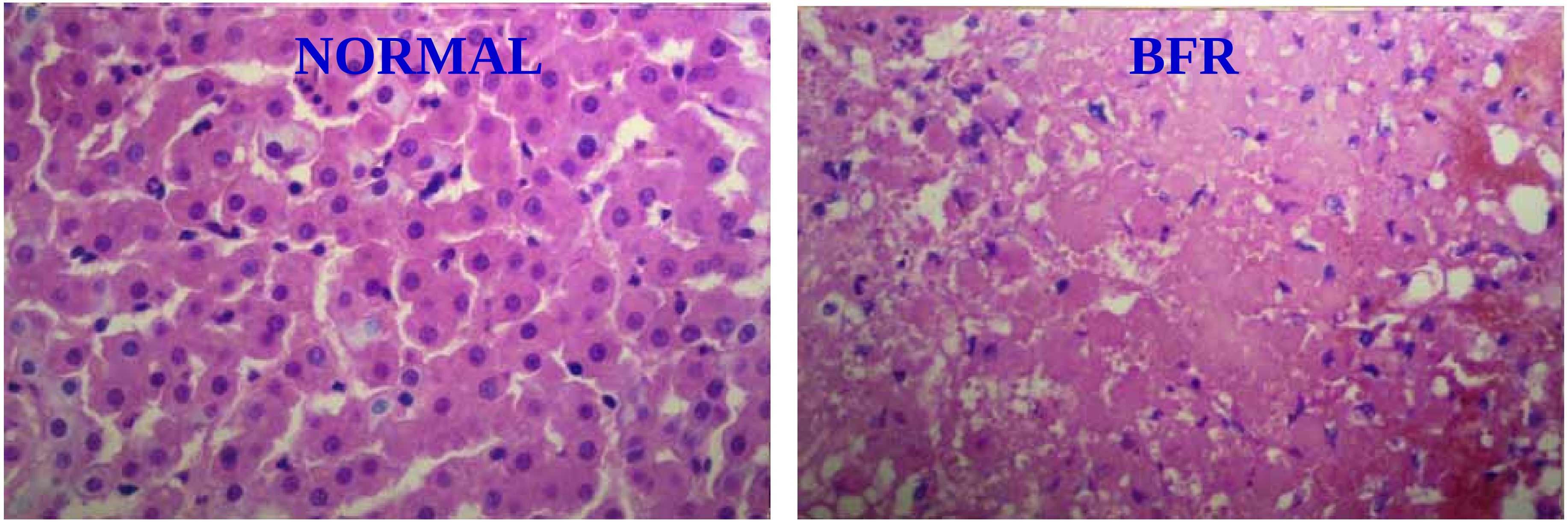


Histopathological change after HIFU (HE×400)

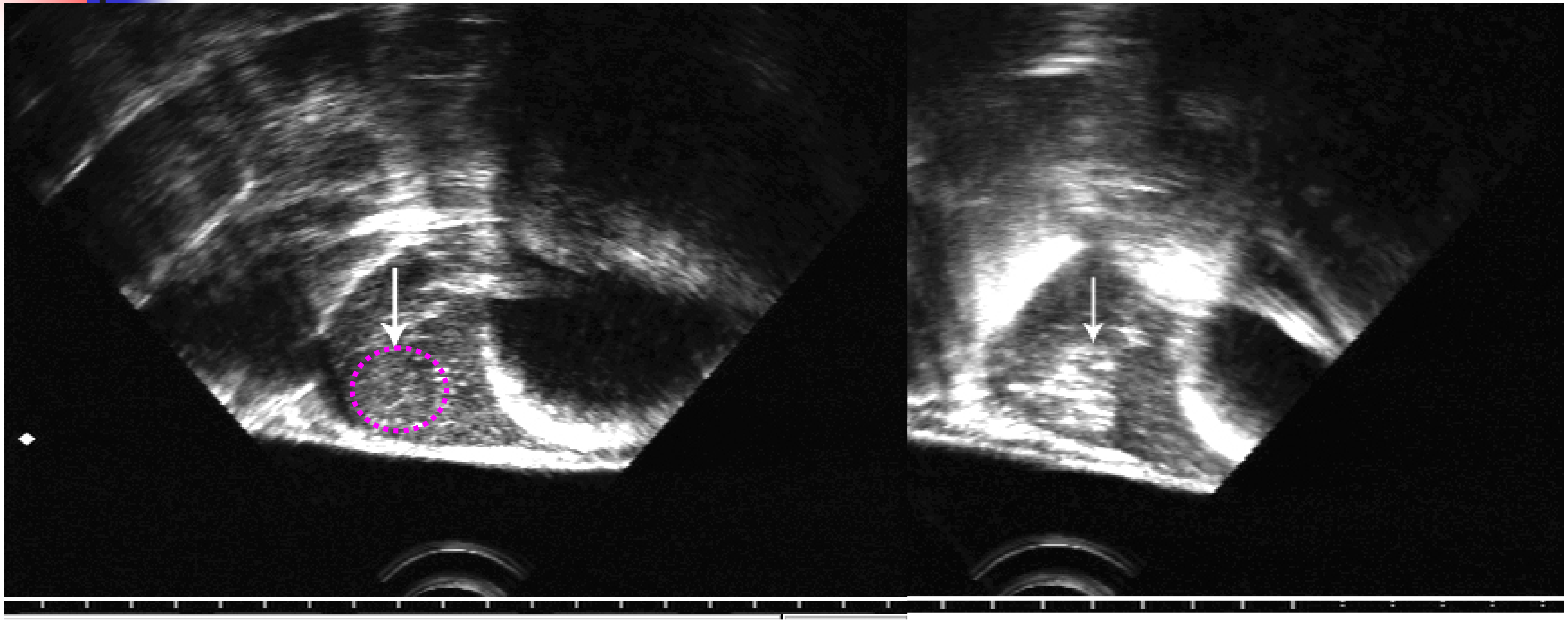
Biological effects of HIFU in *in vivo* tissue/tumor



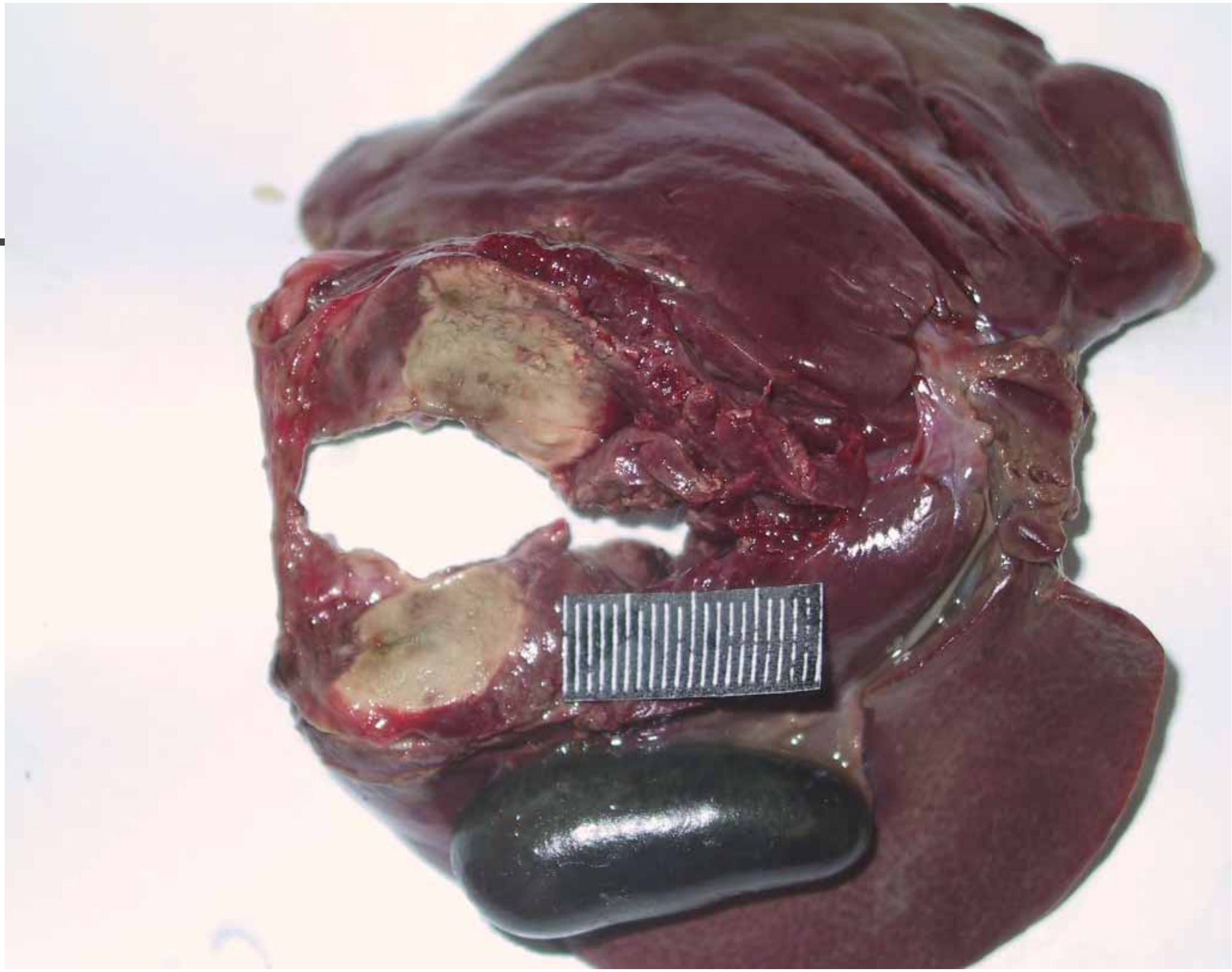
Coagulative necrosis induced in pig liver by HIFU



Histopathological change of the normal and coagulative necrosis induced in pig liver by HIFU (HE ×400)

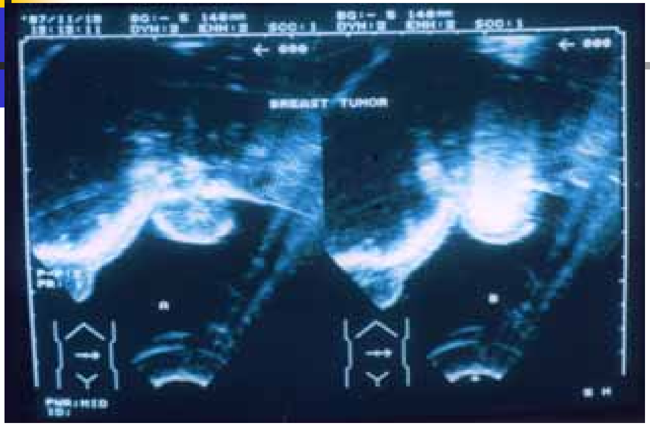

Before HIFU After HIFU

Real time ultrasound monitoring HIFU therapy of rabbit’s liver tumor

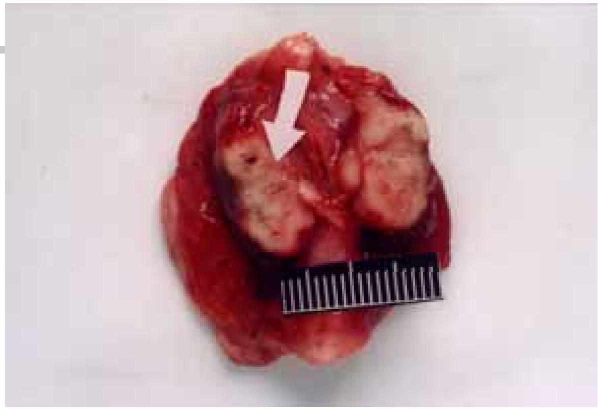


Rabbit liver tumor treated by HIFU（TTC staining）

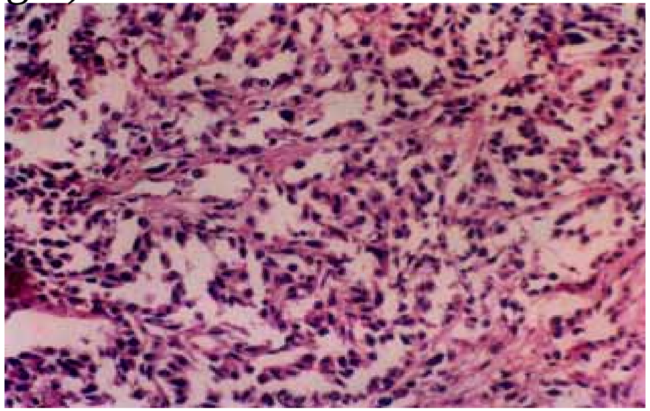
Implanted breast cancer of rabbit



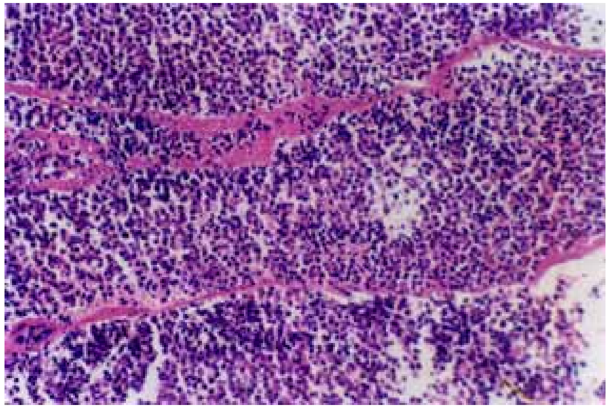
US image before (left) and after (right) HIFU treatment



Implanted breast cancer of rabbit treated by HIFU



Histopathology after HIFU treatment implanted breast cancer (HE ×200)



Histopathology 10 days after HIFU treatment implanted breast cancer (HE ×400)

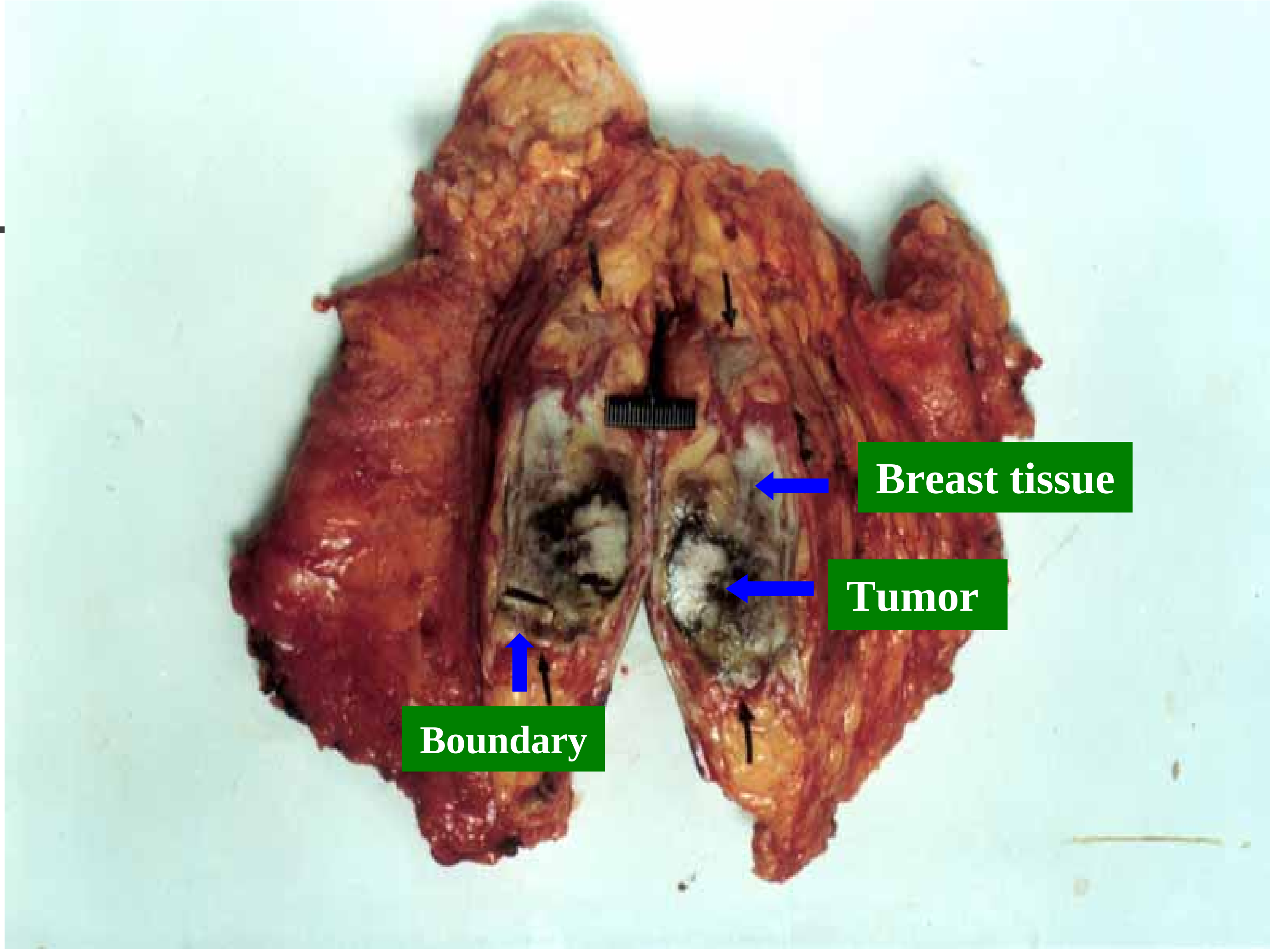
Survival, recrudescence and metastasis after HIFU treatment implanted breast cancer of rabbit

Group	Survival data （d）	Livability in 8 month %	Recrudescence rate %	Metastasis rate %
HIFU	190.6±79.8*△	70*△	20*△	20*△
Surgery	174.4±87.7*§	60*§	30*§	30*§
Control	62.2±18.2△§	0△§		100△§

*HIFU compared with Surgery $p < 0.05$

△HIFU compared with Control $p < 0.05$

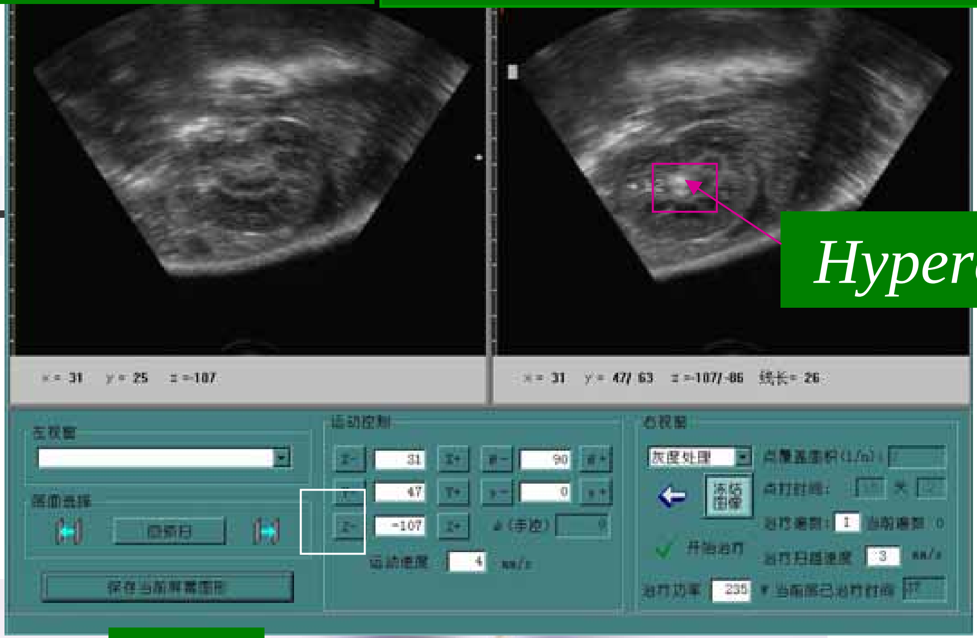
§ Surgery compared with Control $p < 0.05$



Sample got by surgery after HIFU treatment human breast cancer in over- range （1.5-2.0 cm）

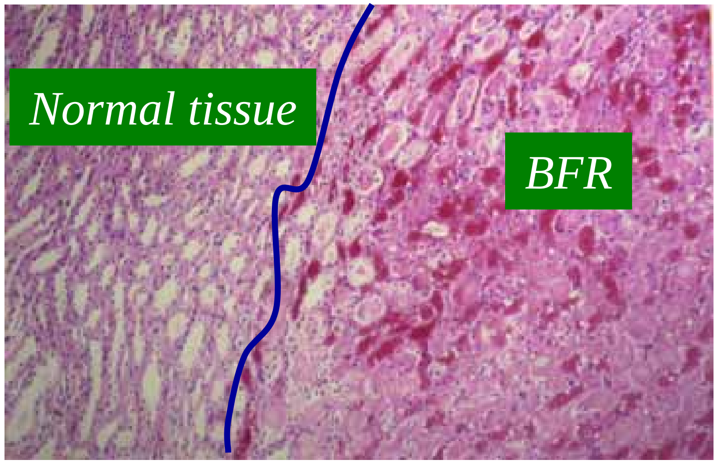
Before HIFU *Immediately after HIFU*

Goat kidney



x = 31 y = 25 z =-107

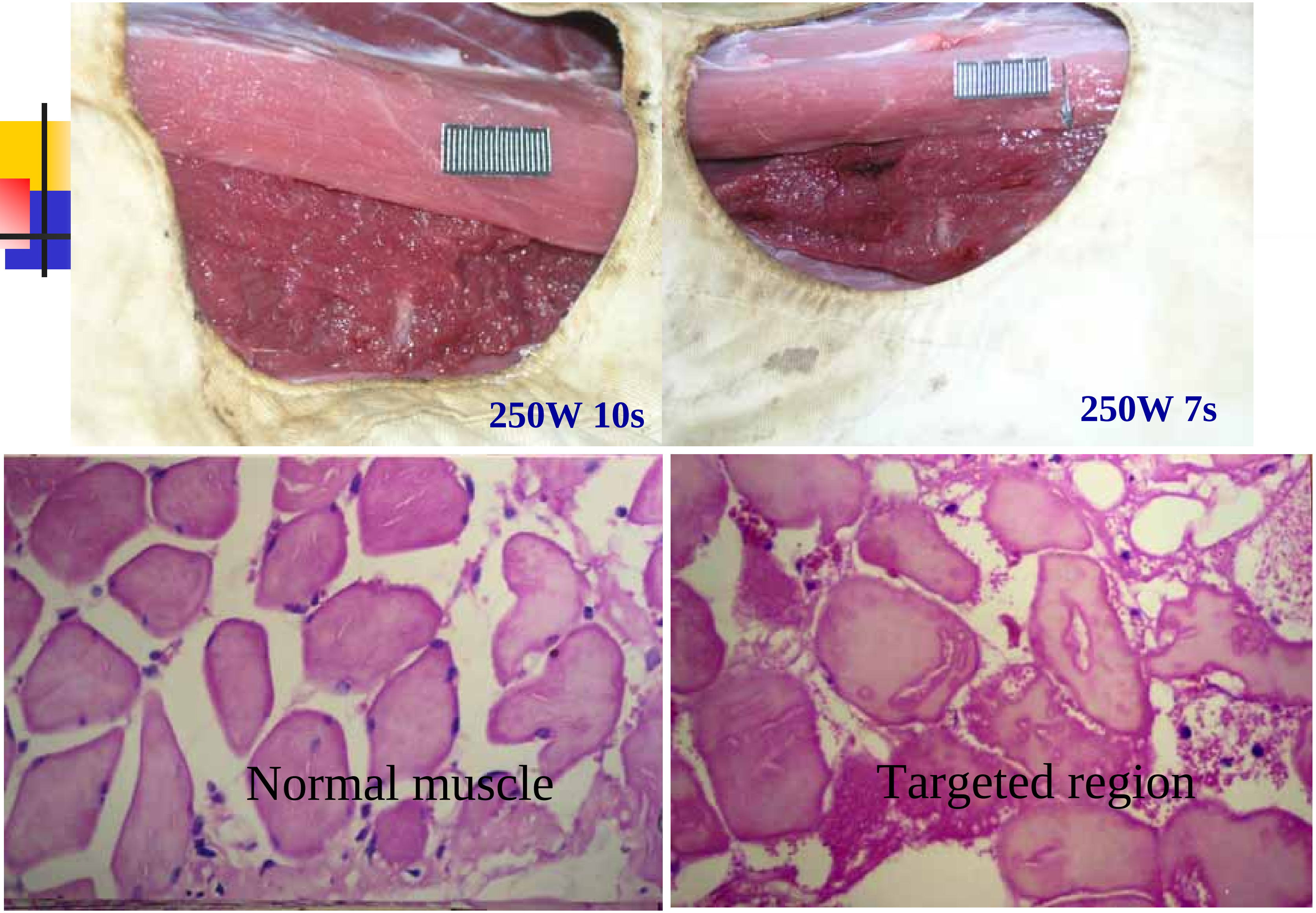
x = 31 y = 47/ 63 z =-107/-86 线长= 26



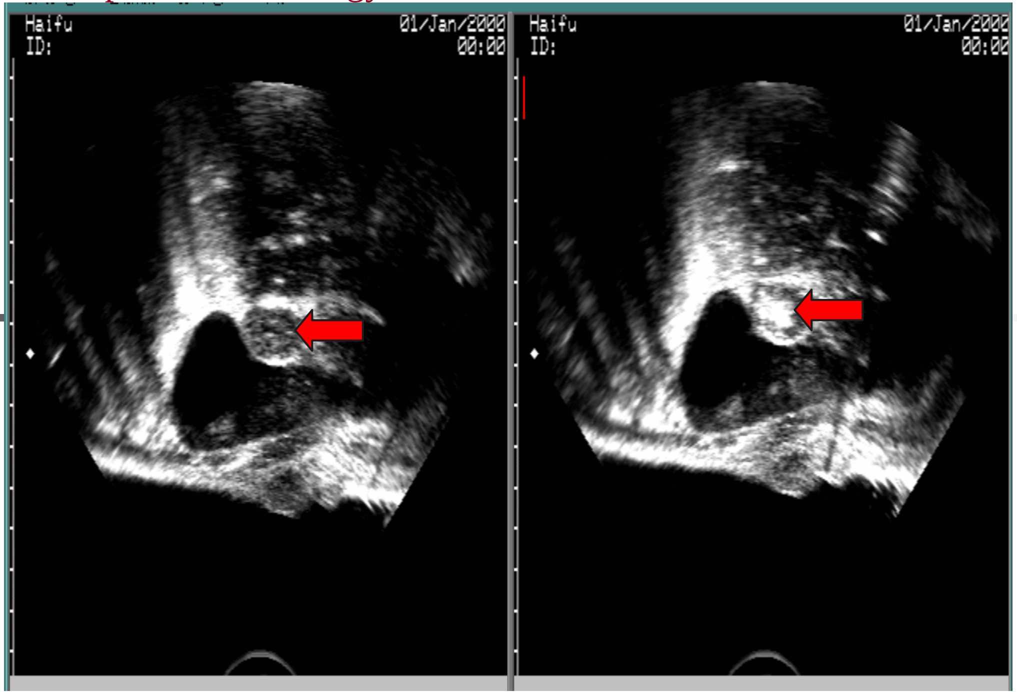
Case of pulmonary metastasis after HIFU treatment implanted VX2 kidney cancer of rabbit

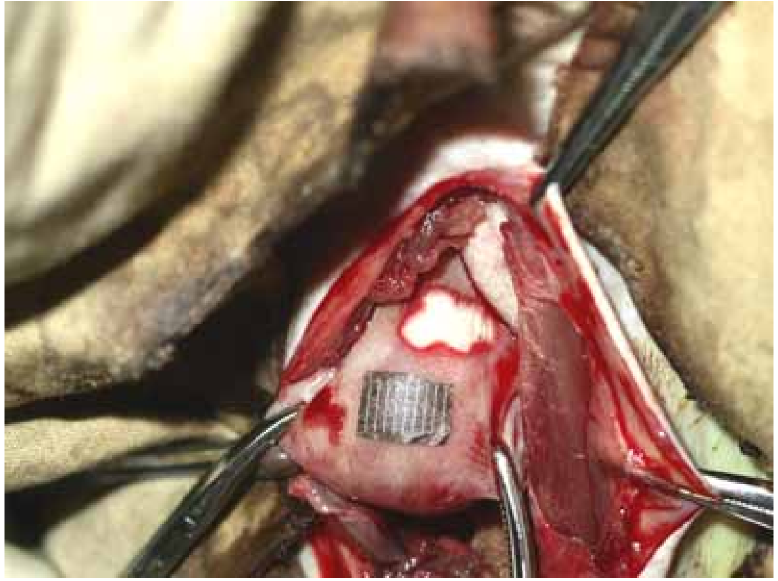
Object	Control	threatment
Recrudescence rate %	100	33*
Number of metastasized nodus	51.69±34.09	6±4.24*

* $p < 0.05$

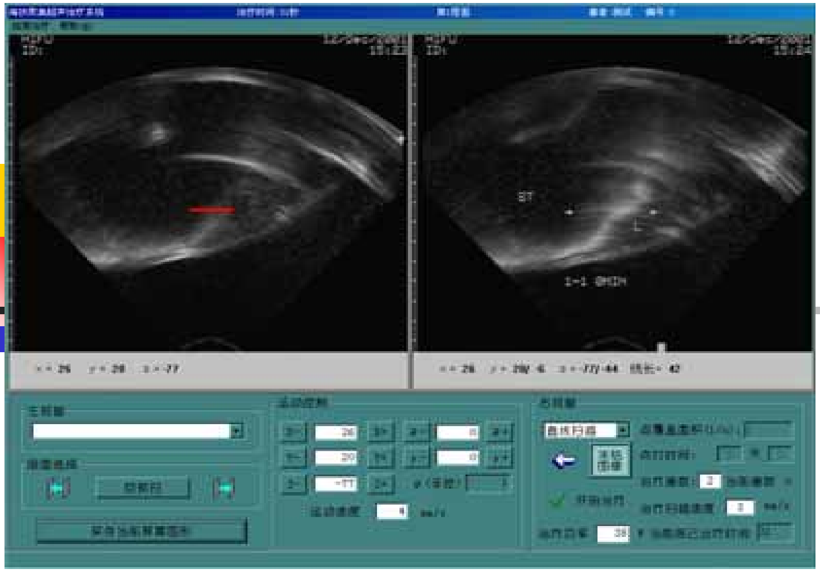


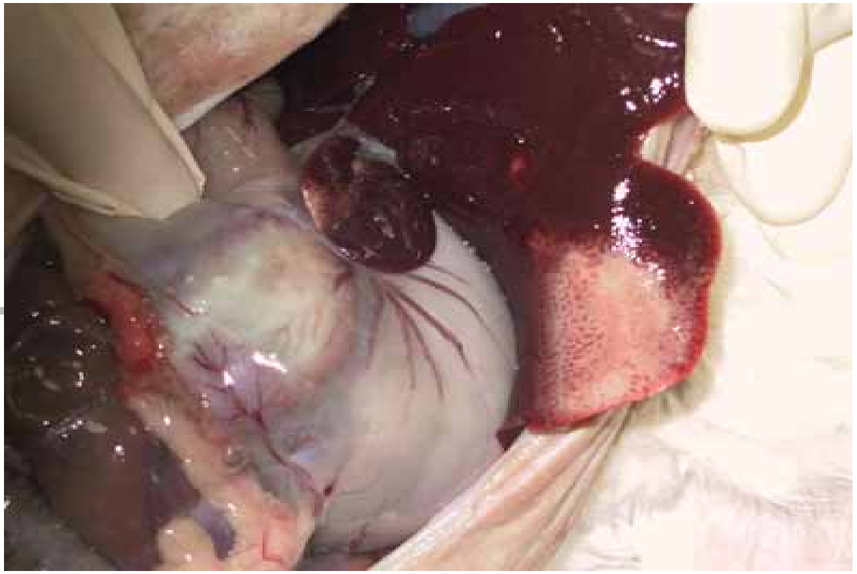
Coagulative necrosis induced in goat muscle by HIFU（top）and histopathology （bottom）

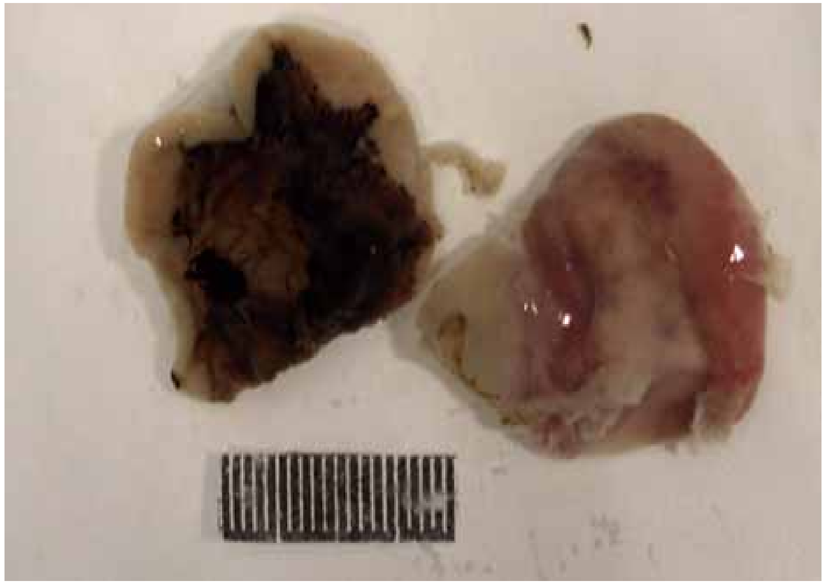




US image before and after HIFU damage the like leiomyoma hyperplasia of mokey’s uterus and coagulation necrosis

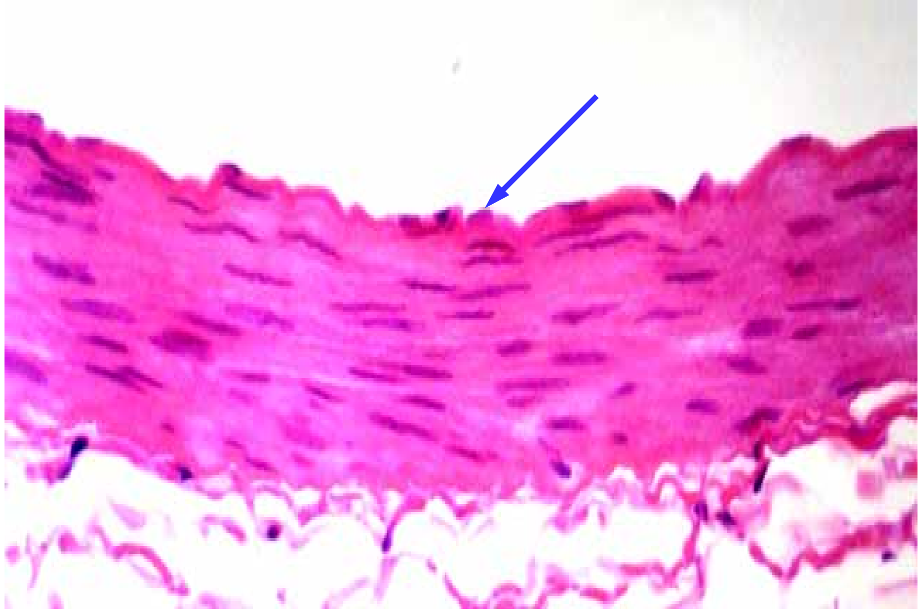




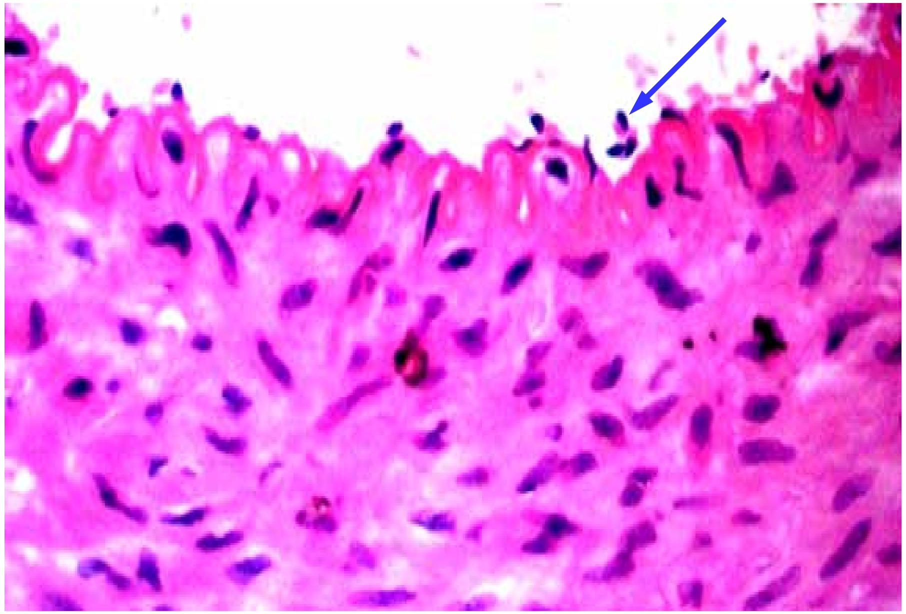


Stomach wall tissue in targeted region
(left :mucosa side, right: serosa side)

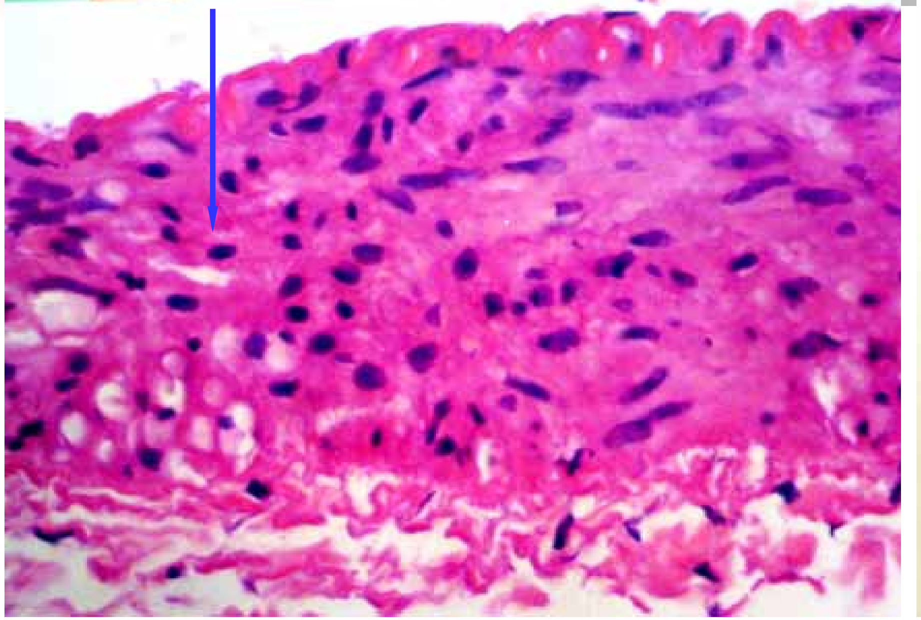
The targeted region tissue tend to be tresis



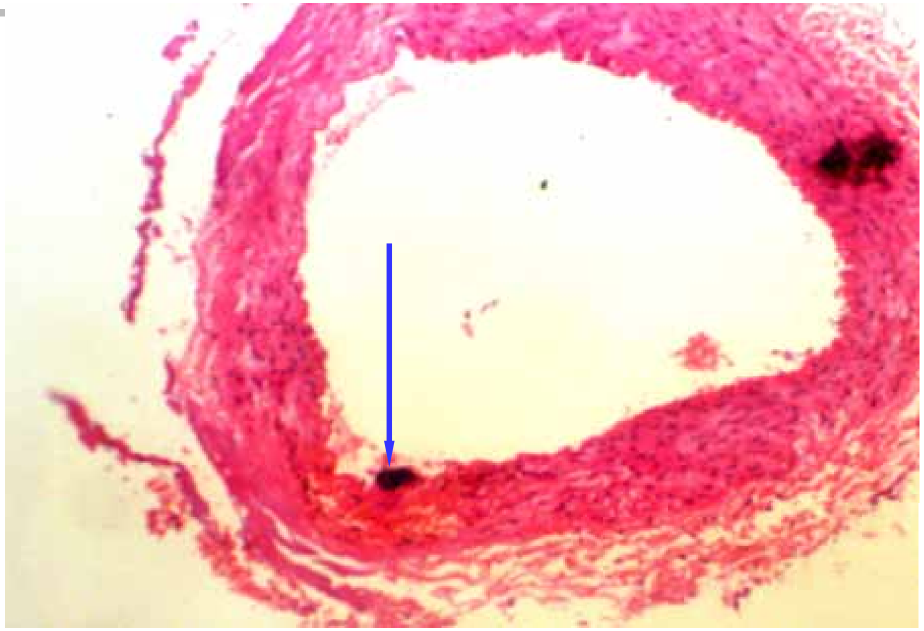
The structure of endothelial cells were integral before HIFU, HE, × 400



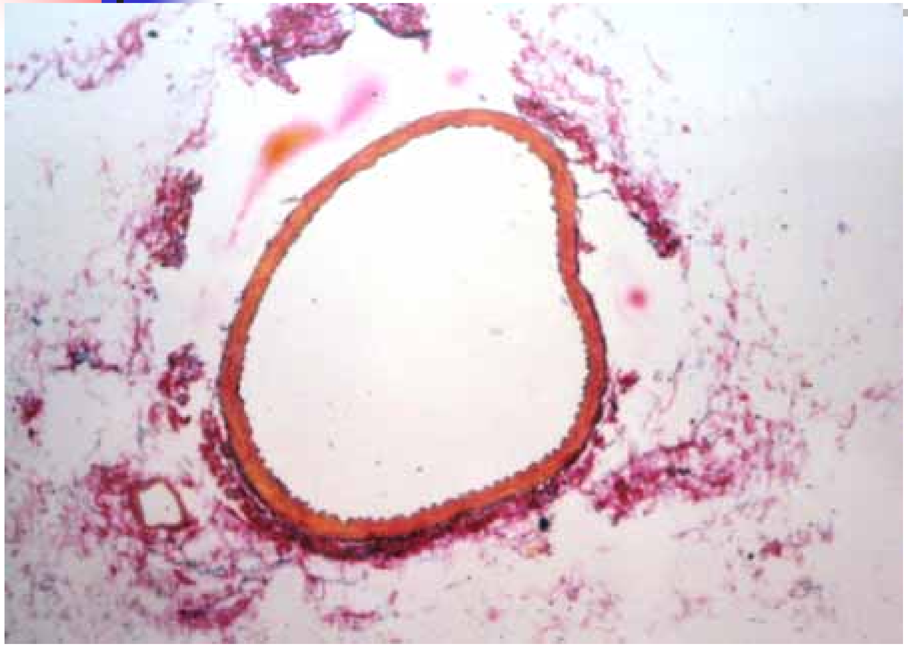
After HIFU irradiation, all endothelial cell were disappeared, HE, × 400



Pyknosis of smooth muscle cells
HE, × 400

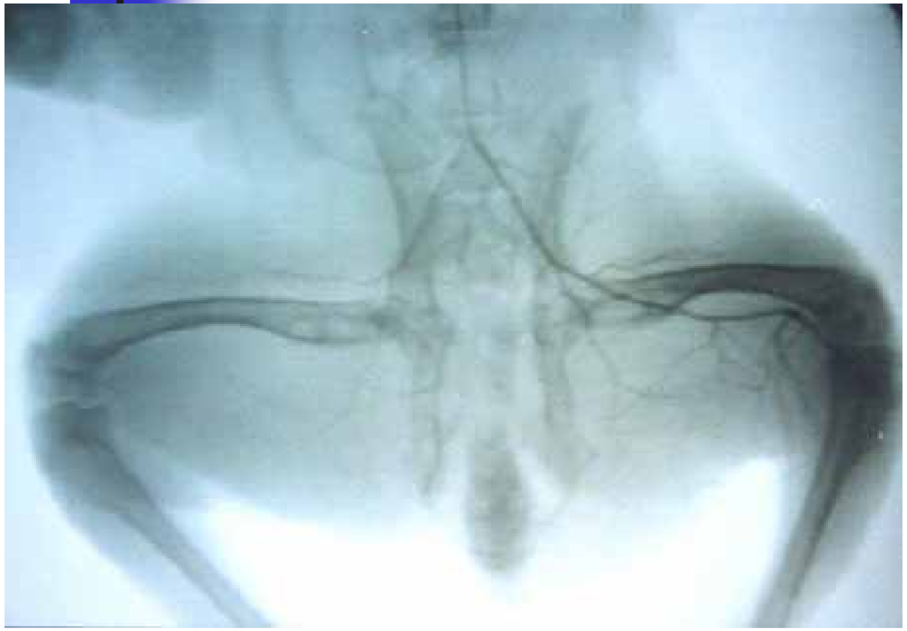


Tiny thrombosis and formed calcification were observed, HE, × 100

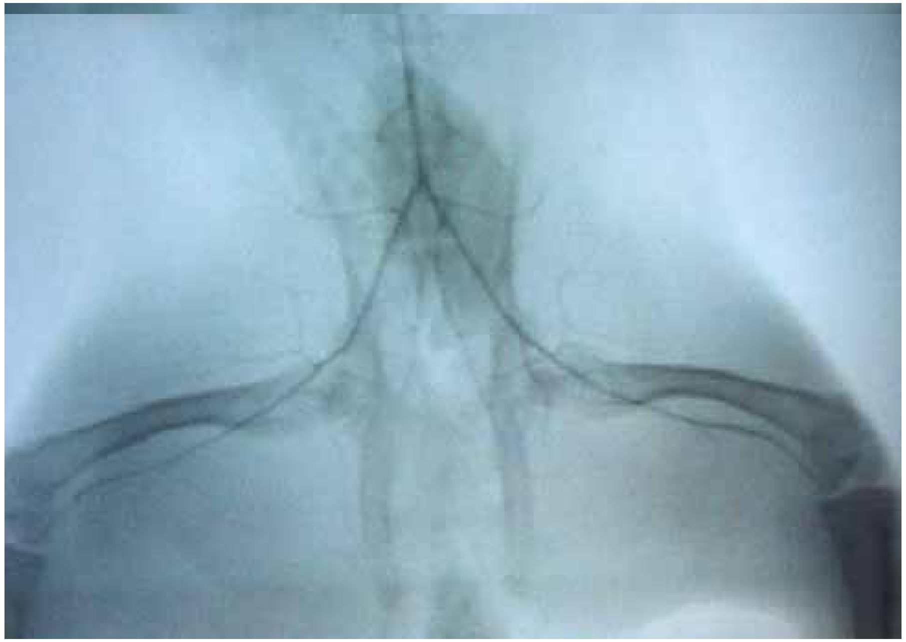


vascular elasticity fibrin was normal before HIFU, × 40

vascular elasticity fibrin collapsed after HIFU， × 40

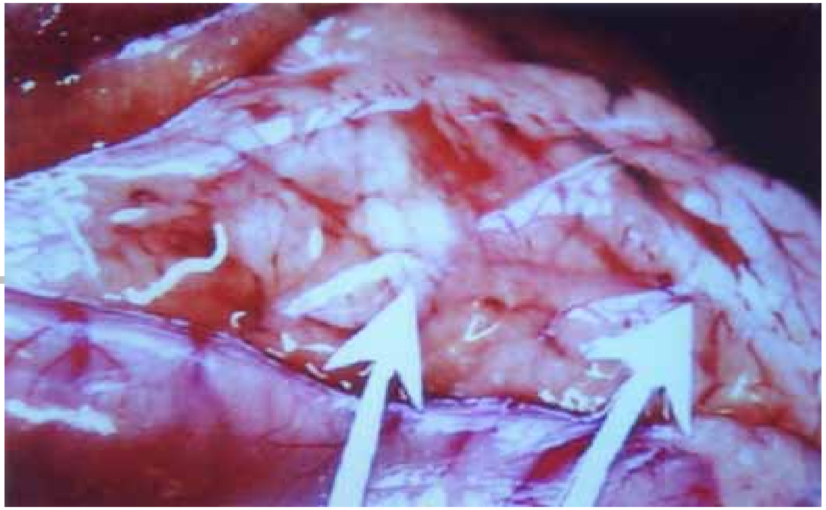


Blood flow was blocked after HIFU immediately,10000W/cm^2

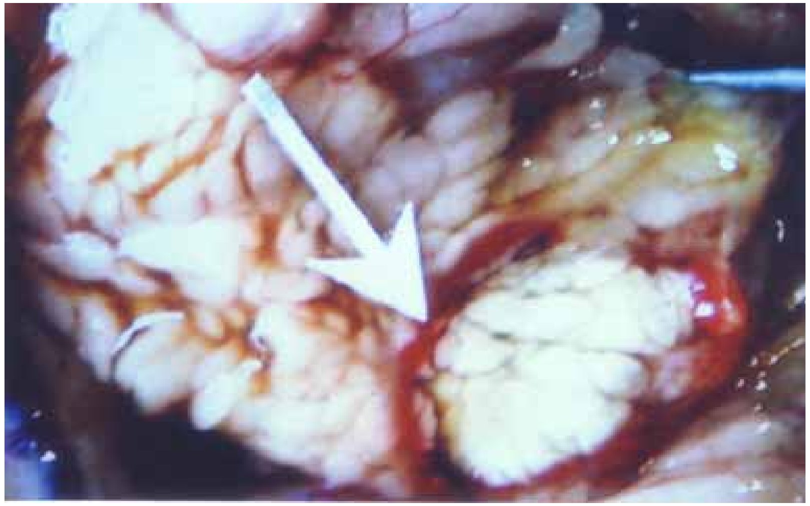


Blood flow obviously after HIFU 3rd,10000W/cm^2

Normal pancreas

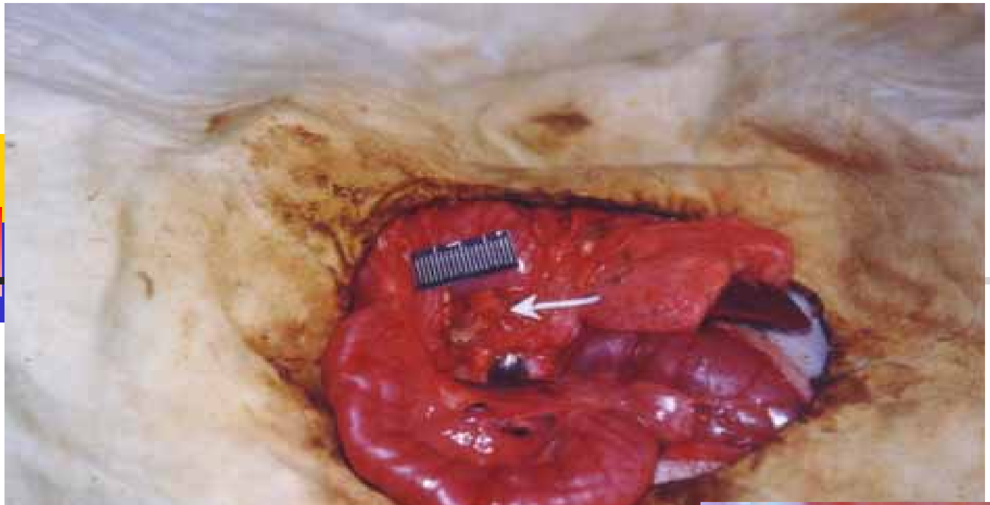


Immediately after HIFU

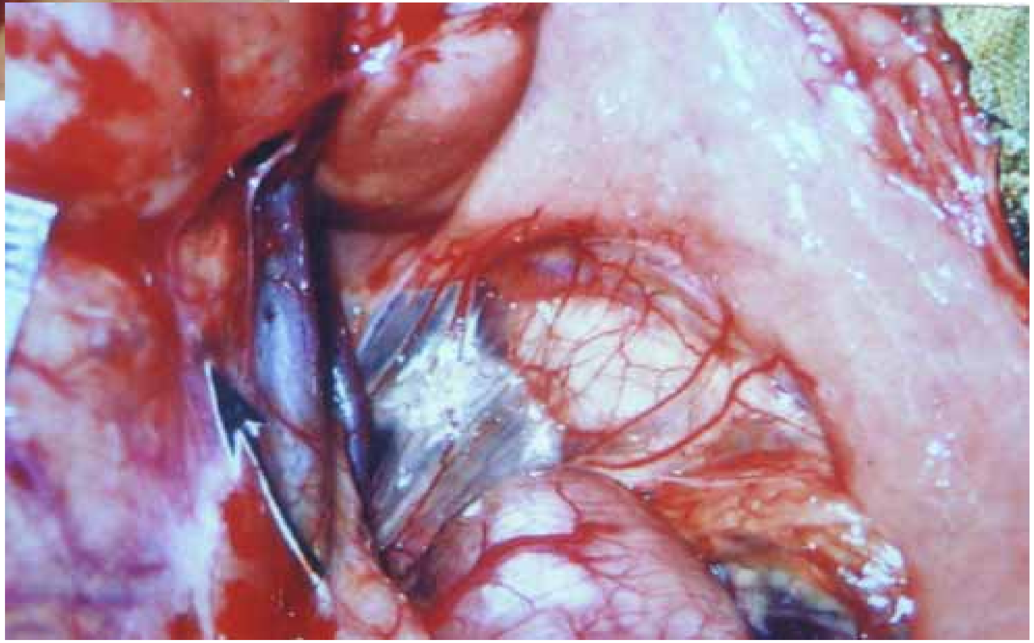


3 days after HIFU treatment

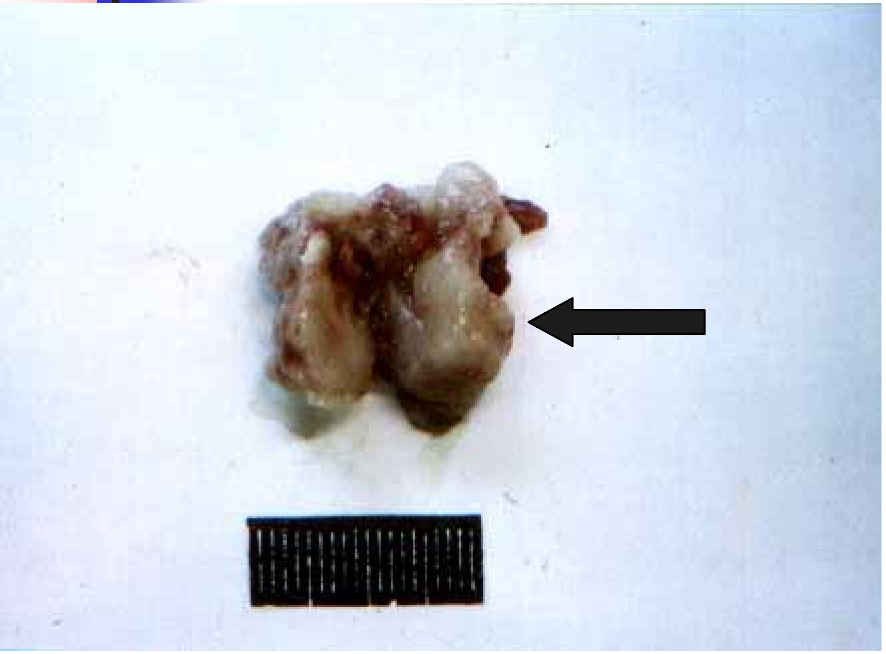
7 days after HIFU



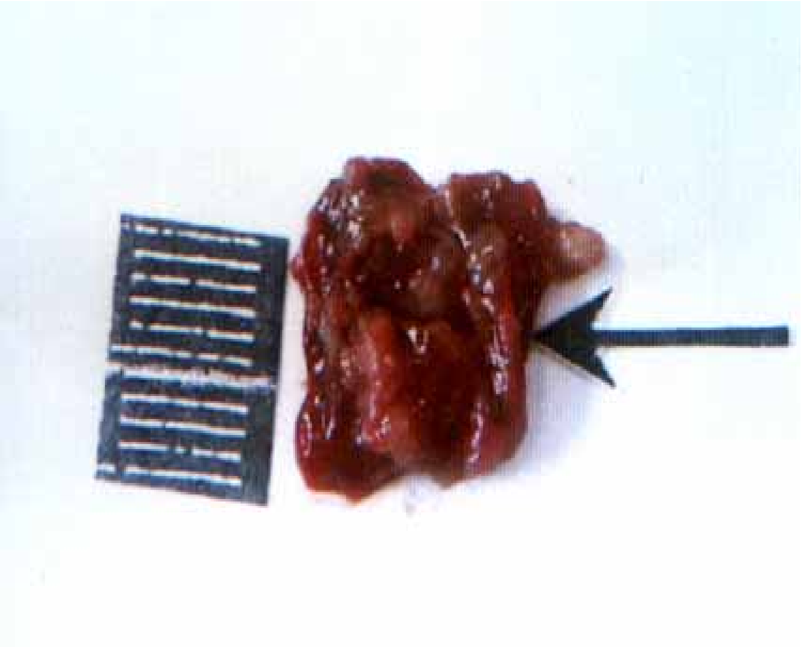
14 days after HIFU



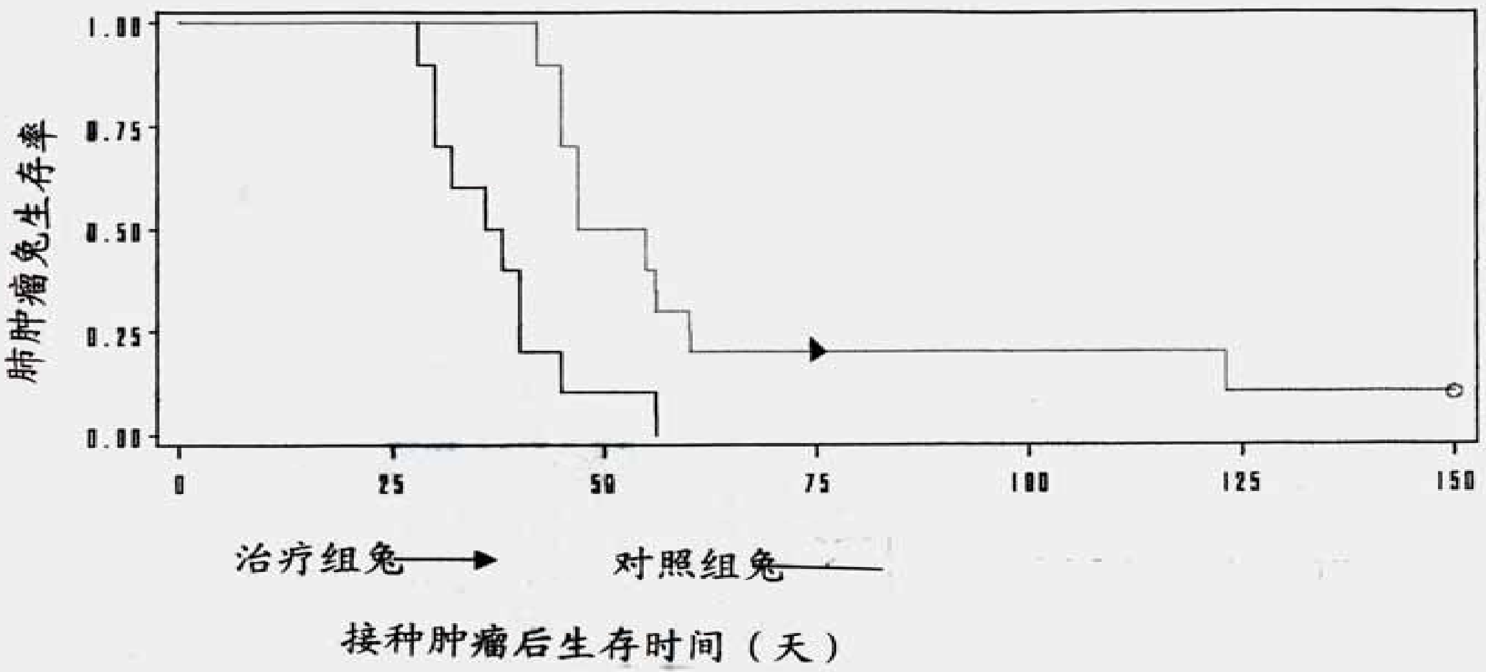
21 days after HIFU



Implanted pulmonary tumour



24h after HIFU



The survival curve of rabbit treated by HIFU and control rabbit

- Bone tumor
- Prostate carcinoma
- Prostate hyperplasia
- Testicle tumor
- Melanoma
- Brain tumor
- Heart
- Spermaduct
- ---------

The mechanism of HIFU treatment tumour

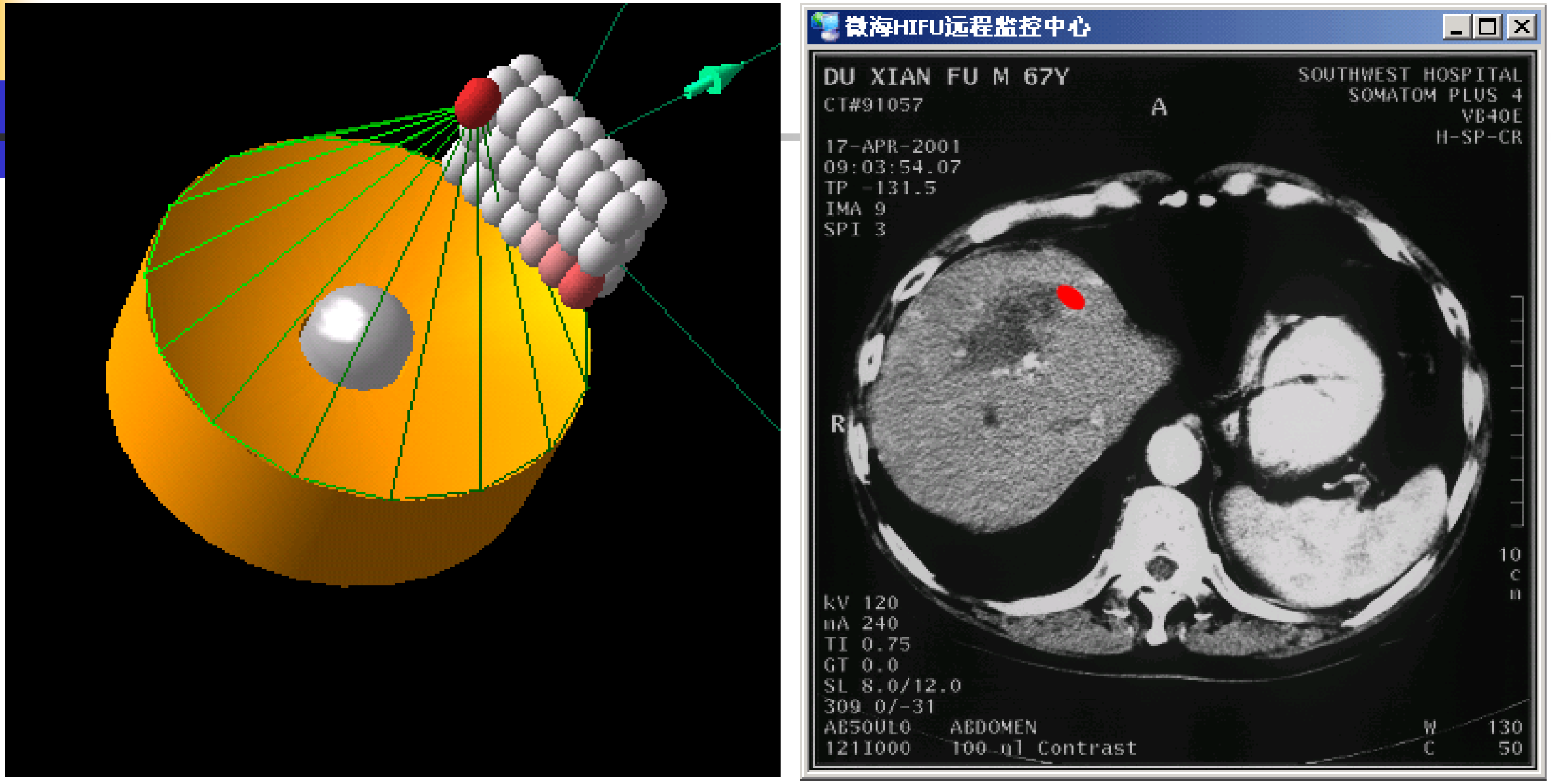
- Thermal effect
- Cavitation effect
- Mechanical effect
- Destroy nutrition vessle of tumor
- Enhance immunity

Objective of the study

- Therapeutic dosage（select parameters）
- Biological effects
- feasibility, safety, and effectiveness
- Treatment planning in clinic
- optimization of device

Chap.8-3
Foundation of dosage delivery for HIFU treatment

Li Faqi
Department of Biomedical Engineering
Institute of Ultrasonic Engineering in Medicine
Chongqing Medical University



HIFU noninvasive ablation of tumor lesion

Key Technologies of HIFU Ablation of Tumour

- Form a well defined and selective coagulative necrosis at focus (Biological Focal Region, BFR)
- Move BFR for complete ablation of a targeted tumour at any shape and evaluation of therapeutic dosage
- Imaging guided therapy procedure
- Clinical protocols

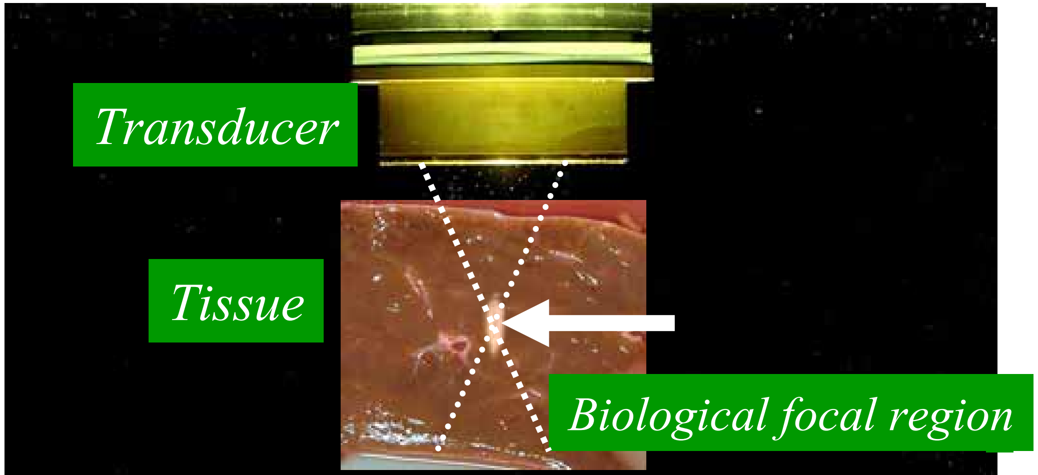
Study on Biological Focal Region (BFR) of HIFU

- **Study of biological effect of ultrasound in 1988.**

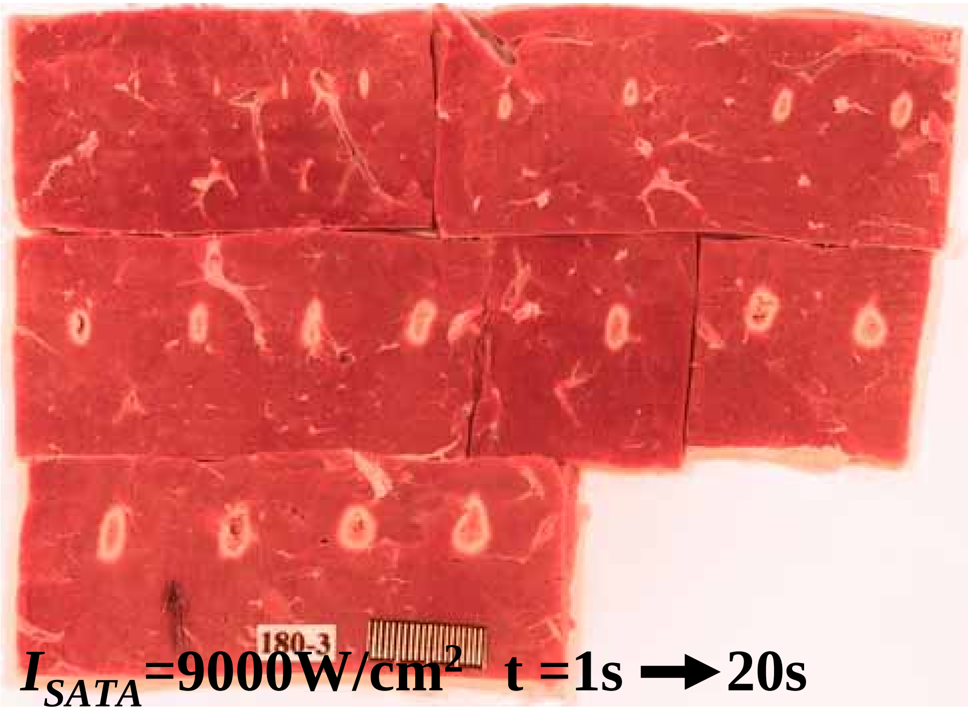
- **First proposed the hypothesis of biological focal region (BFR) of HIFU on fifths symposium of "Academic Association of Sonochemistry of Europe" in 1996.**

- **Wang Zhibiao et al .Targeted damage effect of high intensity focused ultrasound (HIFU) on liver tissues of Guizhou Province miniswine. Ultrasonics Sonochemistry.1997;4:181-182**

- **Wang Zhibiao et al . Study of a "Biological Focal Region"of High Intensity Focused Ultrasound . Ultrasound in Medicine and Biology . 2003;29(4):749-754**

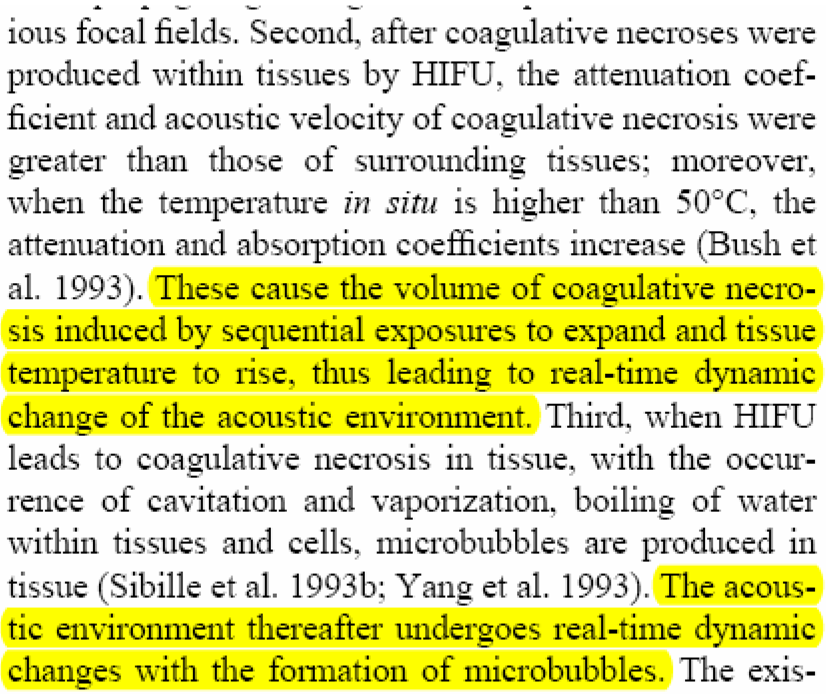


Biological Focal Region (BFR) is proposed relative to AFR, that is, an elliptical coagulative necrosis in tissue caused by the energy deposition of a single exposure of HIFU.



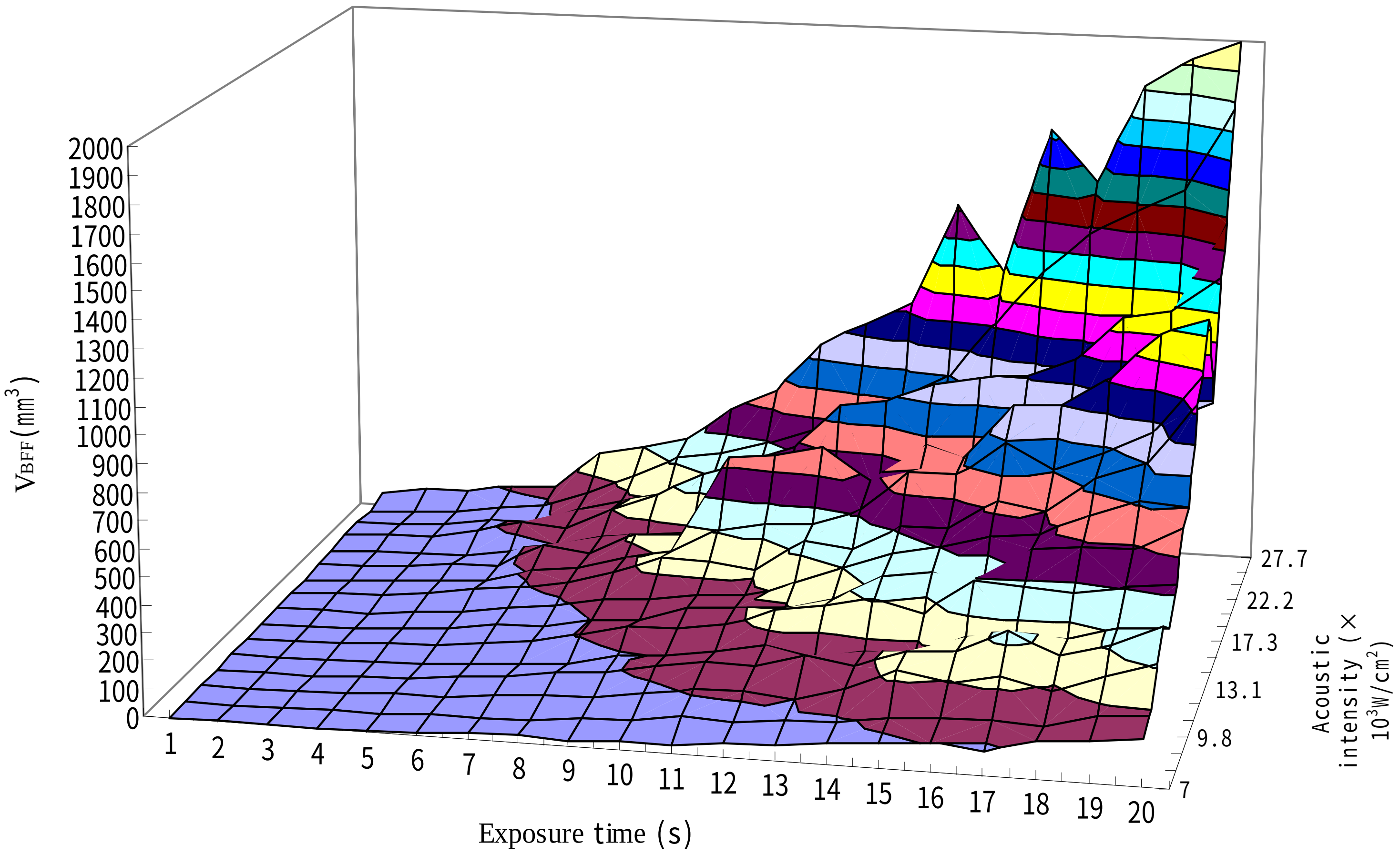
I_{SATA}=9000W/cm^2 t =1s → 20s

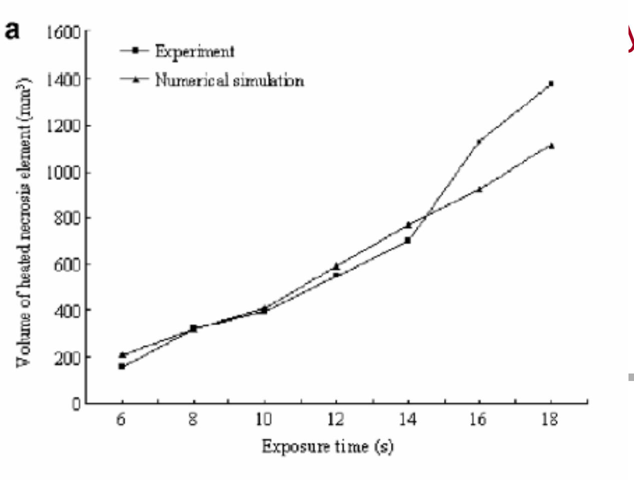
I_{SATA}=25400W/cm^2 t =1s → 20s

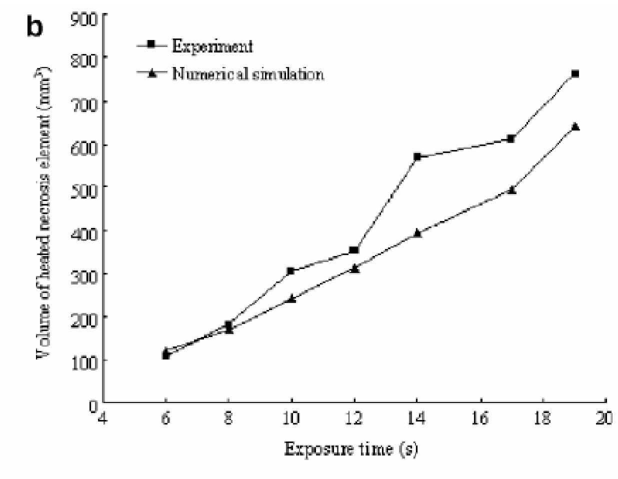


ious focal fields. Second, after coagulative necroses were produced within tissues by HIFU, the attenuation coefficient and acoustic velocity of coagulative necrosis were greater than those of surrounding tissues; moreover, when the temperature *in situ* is higher than 50°C, the attenuation and absorption coefficients increase (Bush et al. 1993). These cause the volume of coagulative necrosis induced by sequential exposures to expand and tissue temperature to rise, thus leading to real-time dynamic change of the acoustic environment. Third, when HIFU leads to coagulative necrosis in tissue, with the occurrence of cavitation and vaporization, boiling of water within tissues and cells, microbubbles are produced in tissue (Sibille et al. 1993b; Yang et al. 1993). The acoustic environment thereafter undergoes real-time dynamic changes with the formation of microbubbles. The exis-

Effect of acoustic intensity and exposure time on BFR







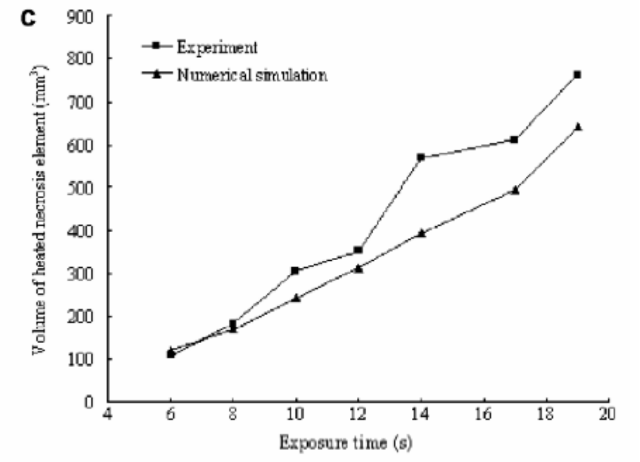


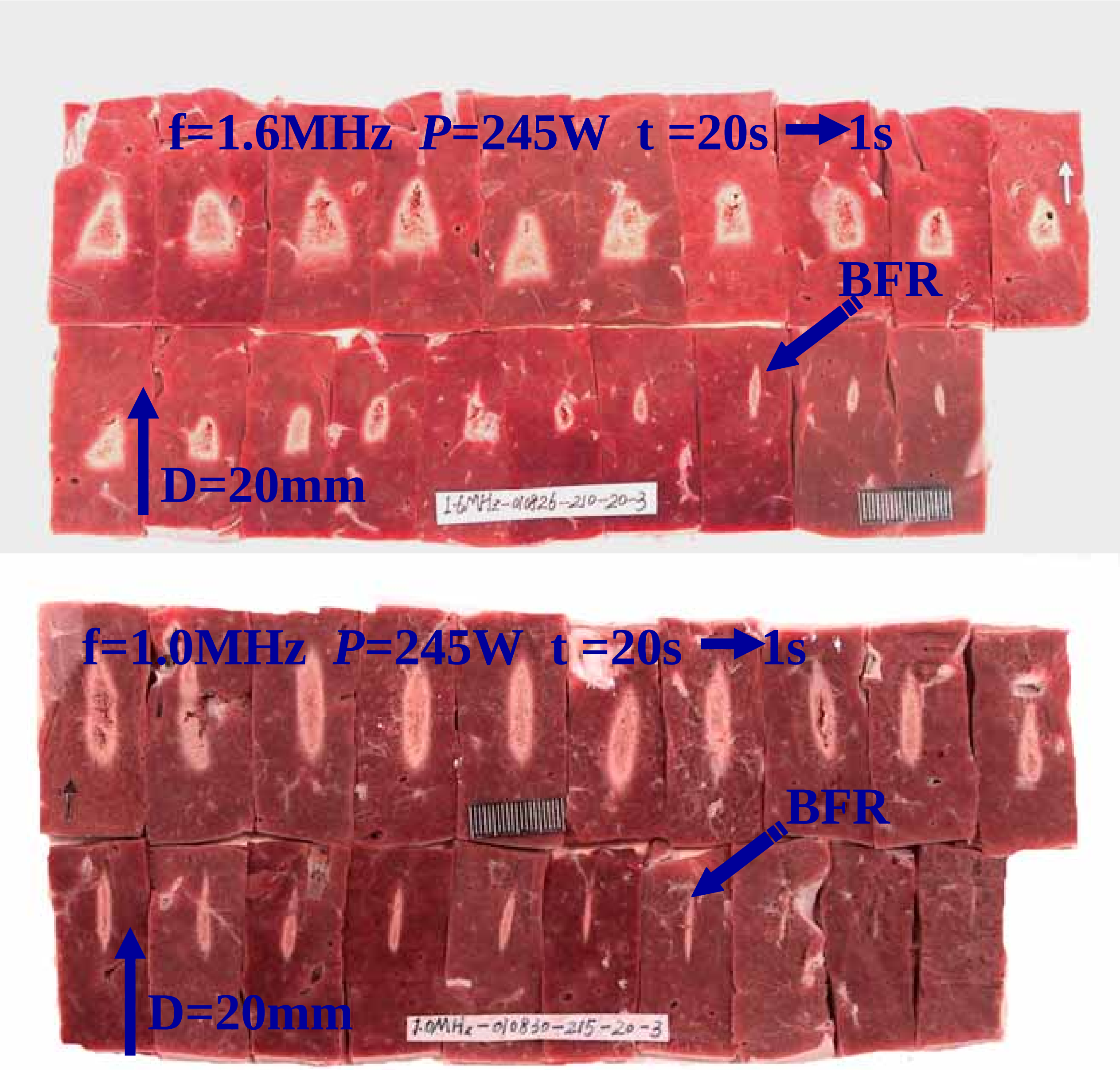
Fig. 2. Comparison between experiment and numerical simulation for the volume of the heated necrotic element induced by HIFU at 2 cm focal depth in in vitro bovine liver. (a) Acoustic intensity $I = 25.4 \times 10^3$ W/cm^2; (b) acoustic intensity $I = 17.3 \times 10^3$ W/cm^2; (c) acoustic intensity $I = 7 \times 10^3$ W/cm^2.

4. Conclusions

(1) The relationship between the heated necrotic element induced by HIFU and the exposure dose can be predicted theoretically, and the theoretical prediction is largely in agreement with the experimental data for low exposures. We can therefore research the HIFU dosimetry using a numerical simulation method.

(2) For accurately predicting the volume and shape of the heated necrotic element, nonlinear sound wave propagation, cavitation should be considered in the numerical simulation.

(3) The nonlinear acoustic effects occurred in HIFU exposure are worthy of further study in both theory and application.



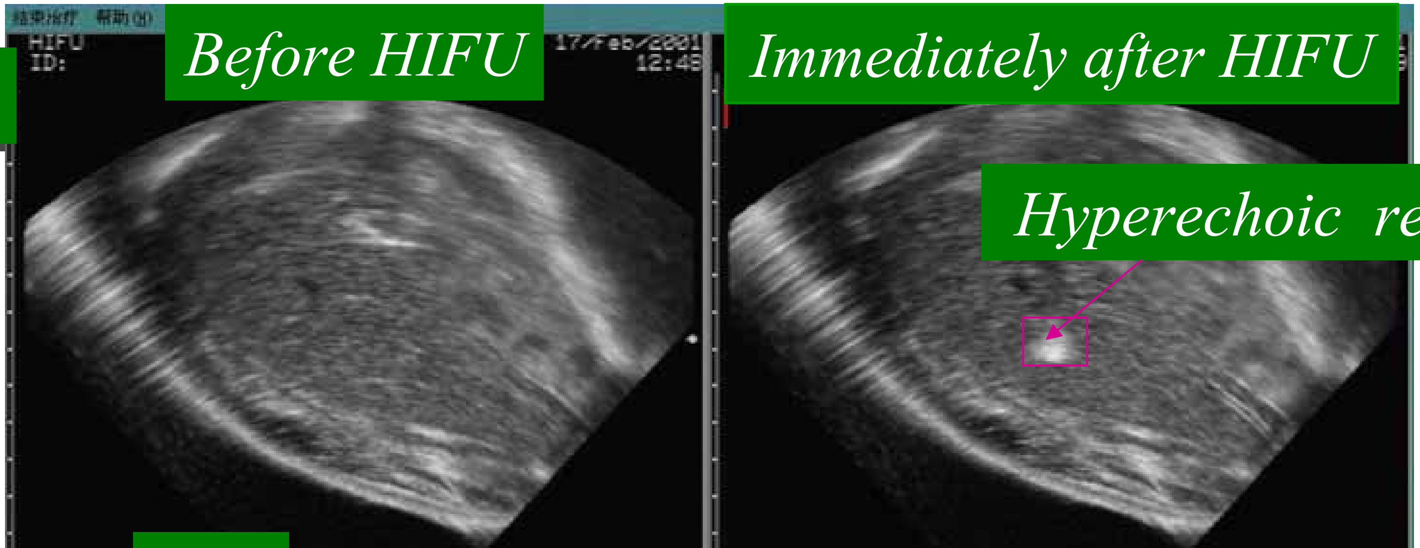
For a same acoustic power and at a same focal depth in tissue, BFR induced in ox liver with HIFU of different frequency and exposure time.

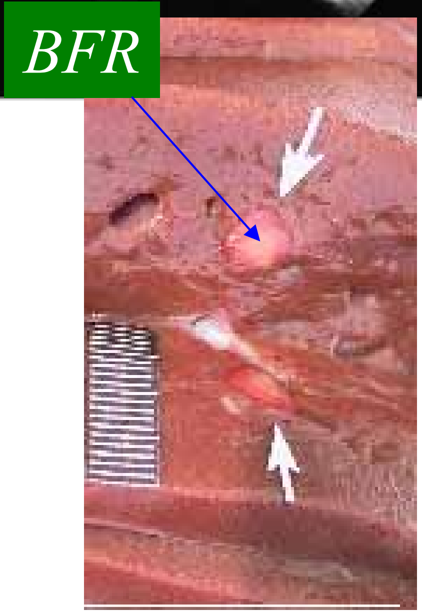
BFR in different focal depth in tissue

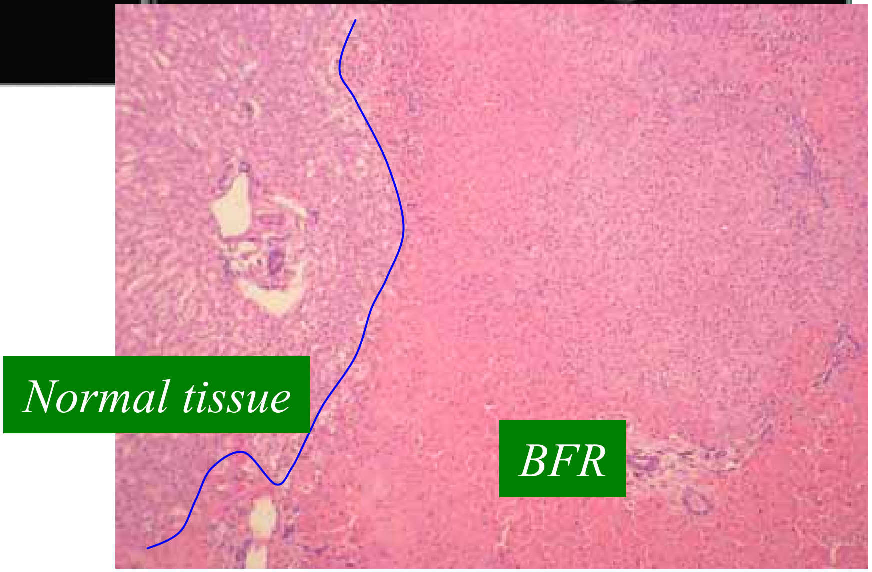
Effect of focal depth in tissue on BFR

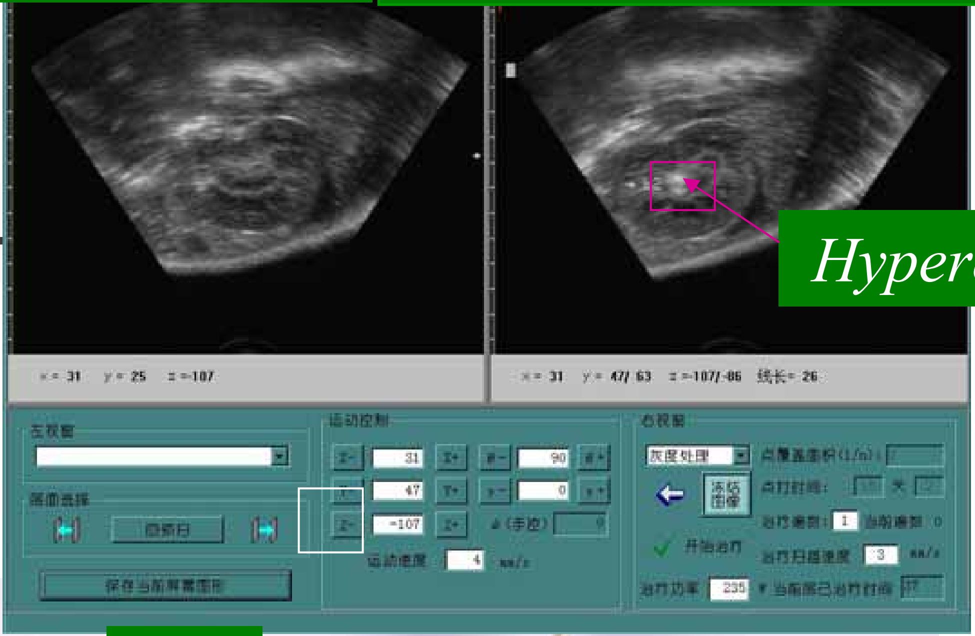
Focal depth (mm) Volume of BFR (mm^3) Exposure time(s)	20	30	40	50	60
1	13.62±1.0	8.74±0.94			
5	55.12±8.91	28.01±3.67	9.36±2.12		
20	805.98±136.18	551.84±22.34	436.49±65.82	352.47±68.94	145.56±15.25
40	3431.8±308.5	1947.0±69.93	1486.5±248.1	982.3±215.7	586.5±154.9
60	7069.46±345.2	5091.2±309.5	3198.2±406.2	1870.7±222.7	1233.4±197.4

Goat liver

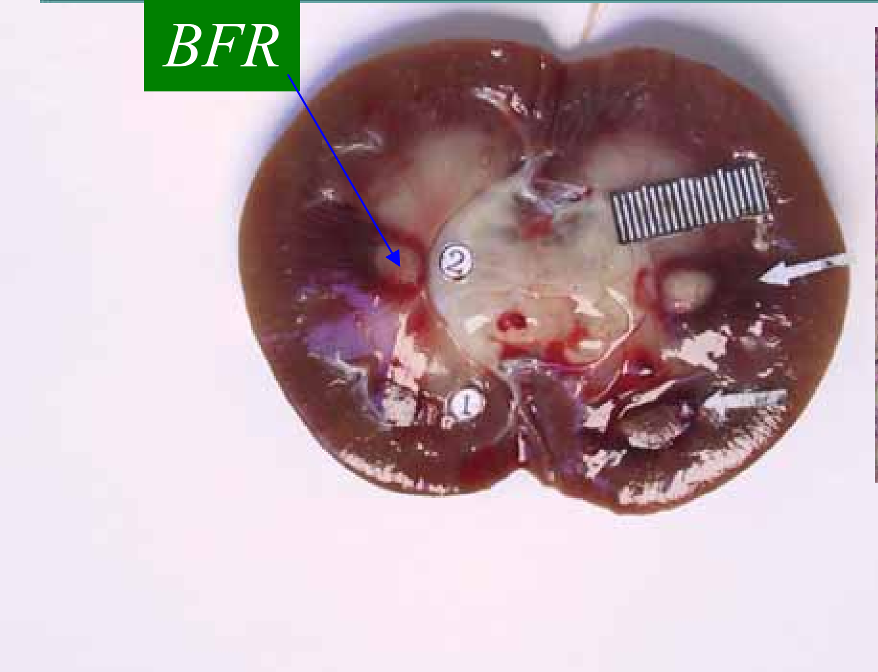

Before HIFU
Immediately after HIFU
Hyperechoic region

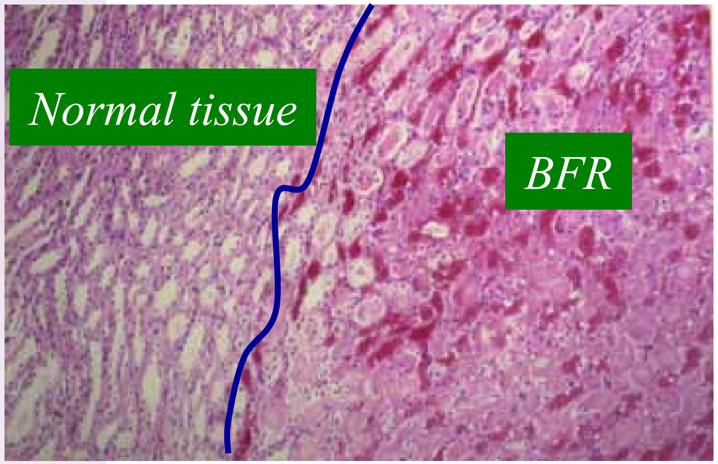

BFR


Normal tissue
BFR


Before HIFU
Immediately after HIFU
Hyperechoic region
x = 31 y = 25 z =-107
x = 31 y = 47/ 63 z =-107/-86 线长= 26
左视窗
剖面选择
运动控制
右视窗
灰度处理
冻结图像
开始治疗
运动速度 4 mm/s
治疗功率 235 W

Goat kidney

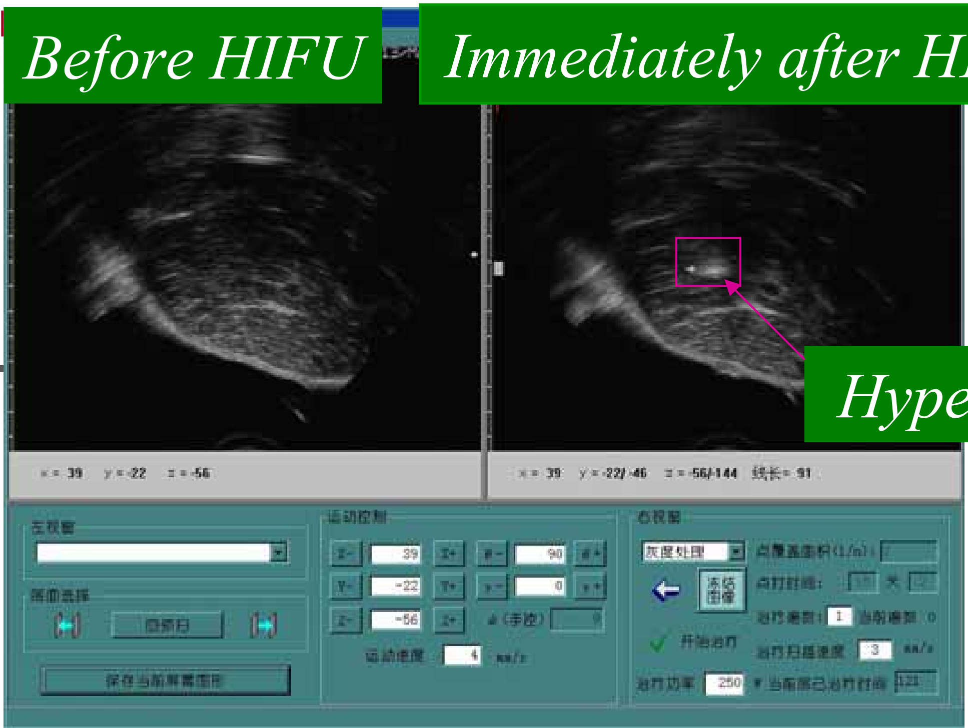

BFR
②
①


Normal tissue
BFR

Before HIFU

Immediately after HIFU

Goat muscle



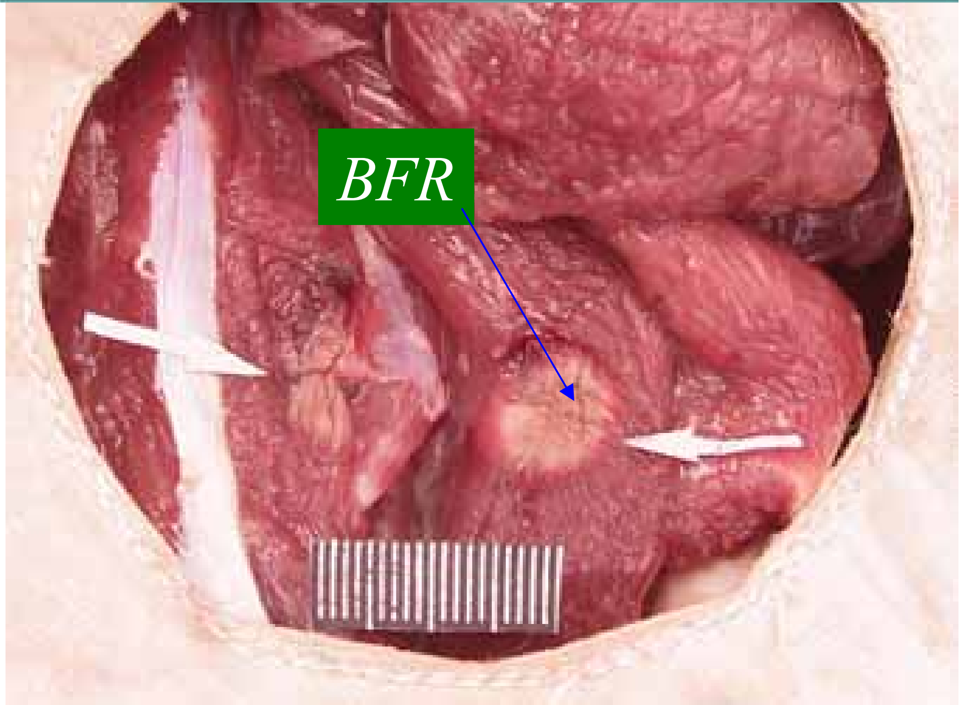
x = 39 y = -22 z = -56

x = 39 y = -22/-46 z = -56/-144 线长= 91

运动速度 4 mm/s

治疗功率 250 W

Hyperechoic region



BFR

Effect of tissue type on BFR

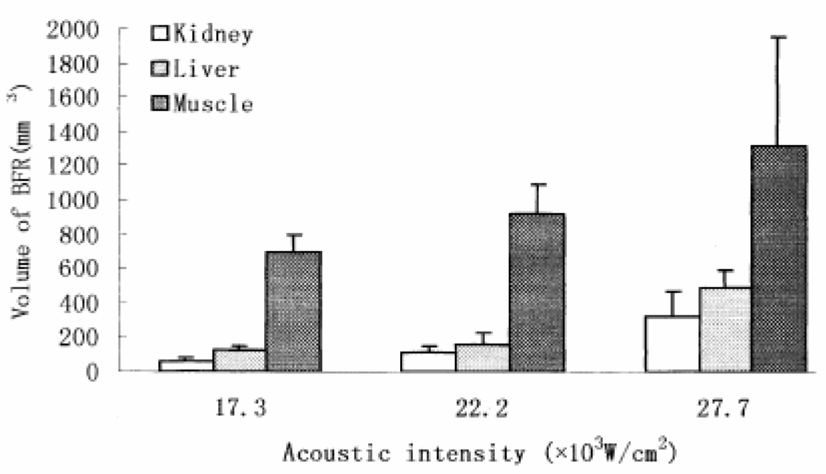
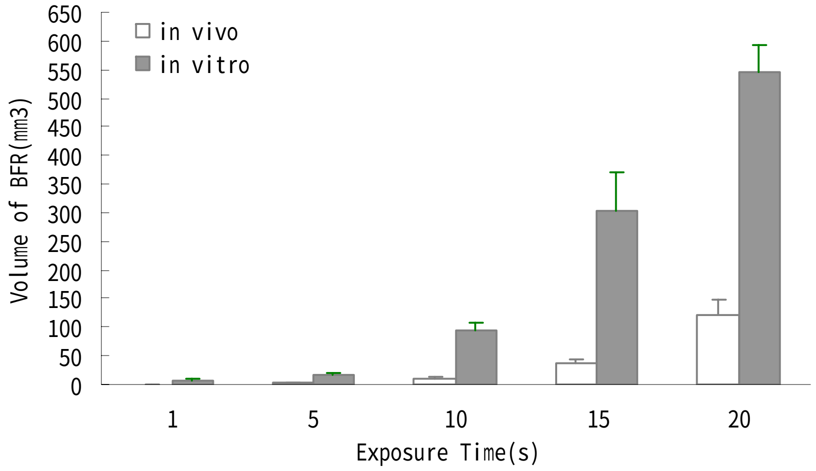
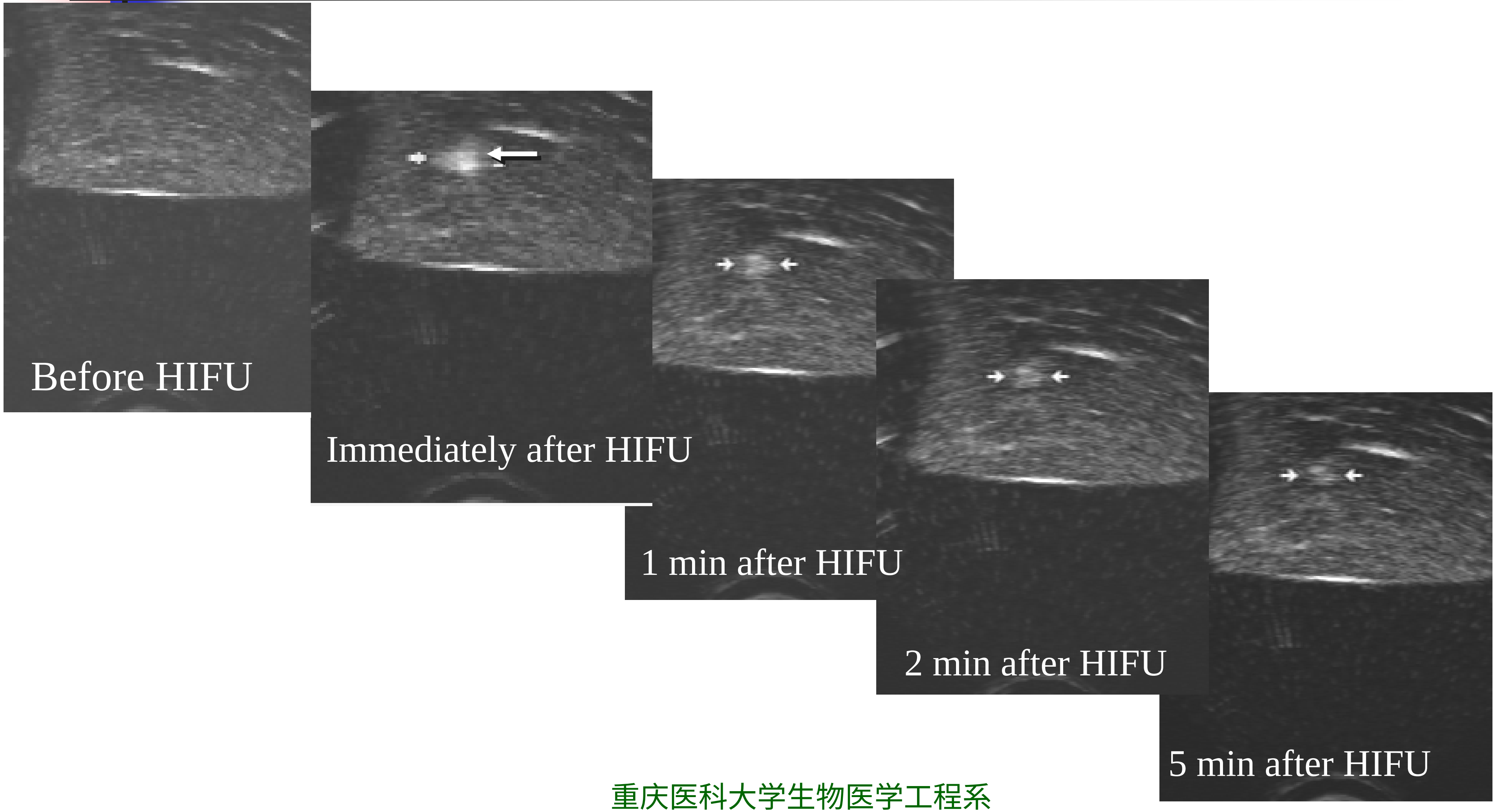


Fig. 6. Volumes of BFRs produced at the same irradiation depth of 40 mm in pig liver, kidney and muscle *in vivo* for different acoustical intensities (17.3×10^3, 22.2×10^3, 27.7×10^3 W/cm^2) and a constant exposure time of 20 s.



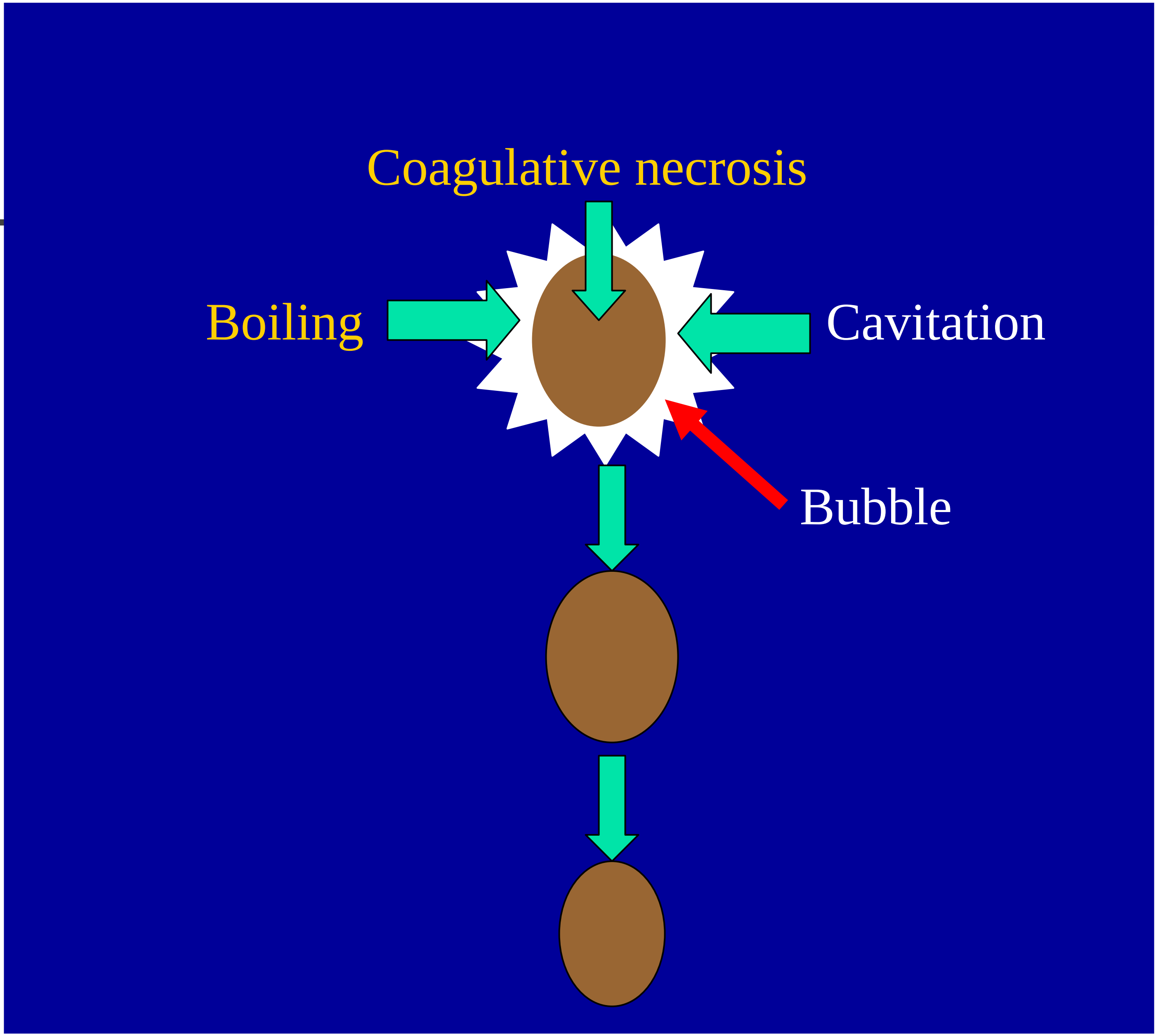
Volume of BFRs produced at the same irradiation depth of 40mm in *in vitro* and *in vivo* liver for same intensity 17.3×10^3 W/cm2 and different exposure time.

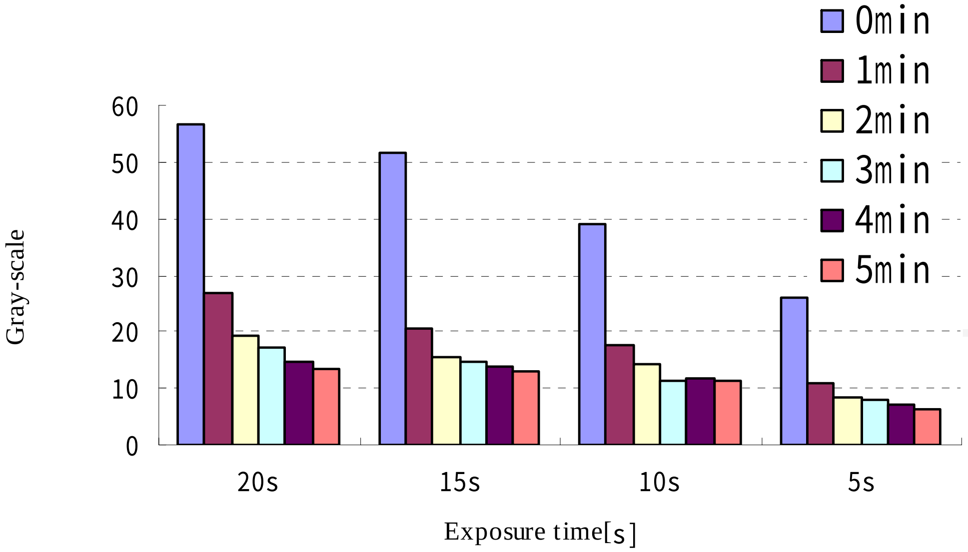
Real time US monitoring of BFR



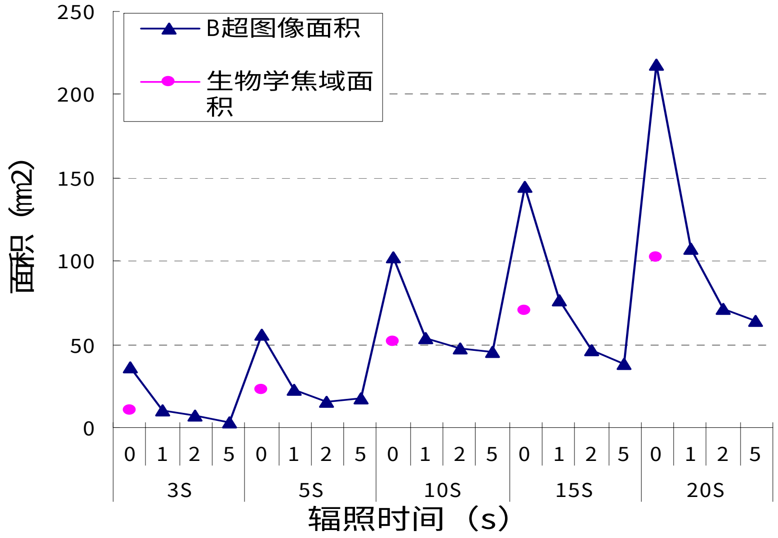
Acoustic basic of monitoring using US image

- ❑Coagulative necrosis
- ❑Temperature rise
- ❑Bubble resulted from boiling and cavitation

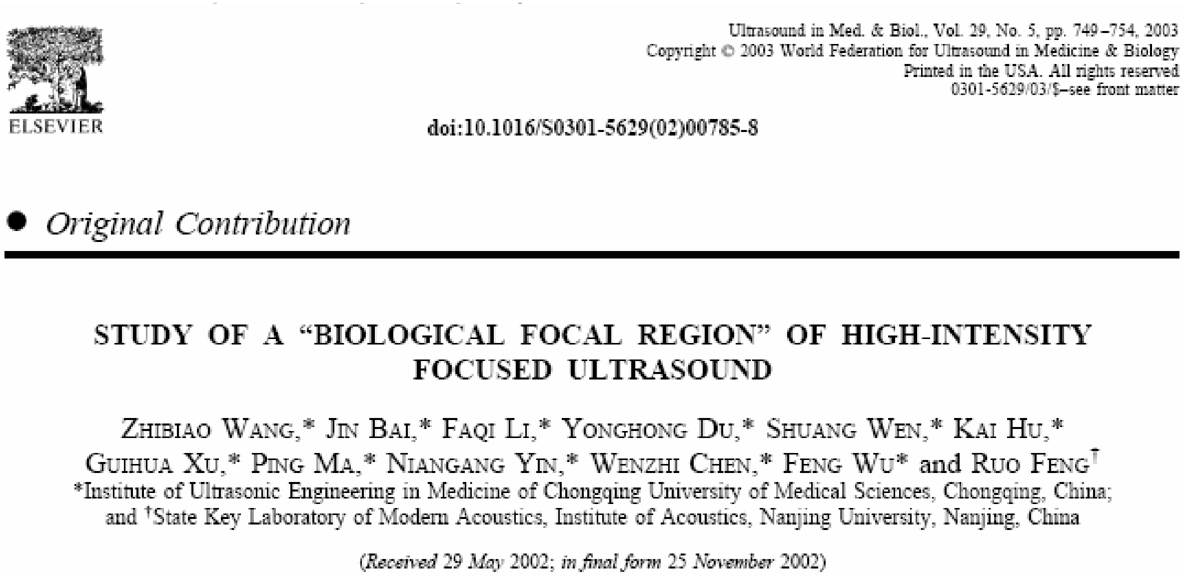

Coagulative necrosis
Boiling
Cavitation
Bubble



The gray values of 1min, 2min, 3min, 4min, 5min after HIFU



The relationship between area of ultrasound imaging and BFR after HIFU



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0301-5629/03/$–see front matter

doi:10.1016/S0301-5629(02)00785-8

● *Original Contribution*

STUDY OF A “BIOLOGICAL FOCAL REGION” OF HIGH-INTENSITY FOCUSED ULTRASOUND

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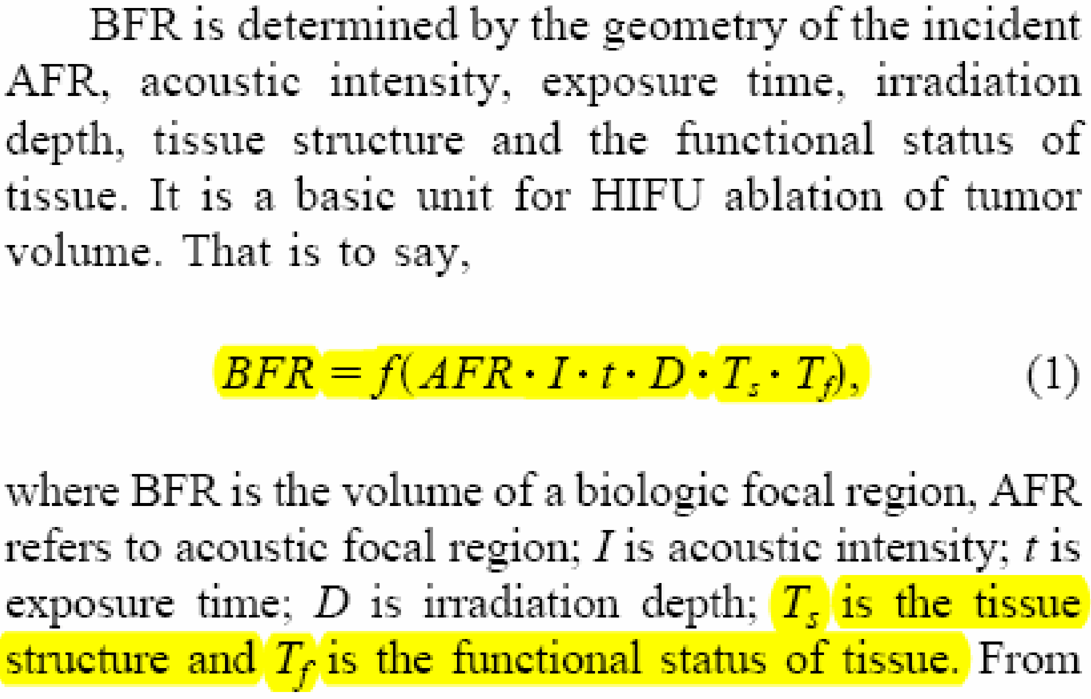
(*Received* 29 *May* 2002; *in final form* 25 *November* 2002)



BFR is determined by the geometry of the incident AFR, acoustic intensity, exposure time, irradiation depth, tissue structure and the functional status of tissue. It is a basic unit for HIFU ablation of tumor volume. That is to say,

$$BFR = f(AFR \cdot I \cdot t \cdot D \cdot T_s \cdot T_f), \qquad (1)$$

where BFR is the volume of a biologic focal region, AFR refers to acoustic focal region; I is acoustic intensity; t is exposure time; D is irradiation depth; T_s is the tissue structure and T_f is the functional status of tissue. From

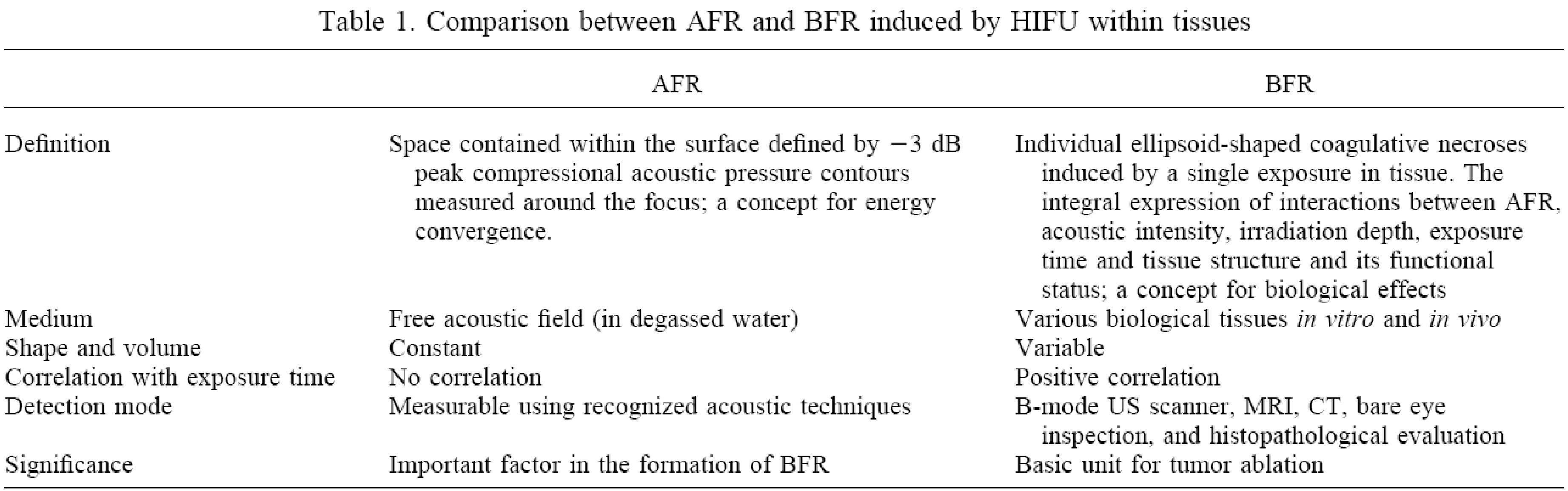
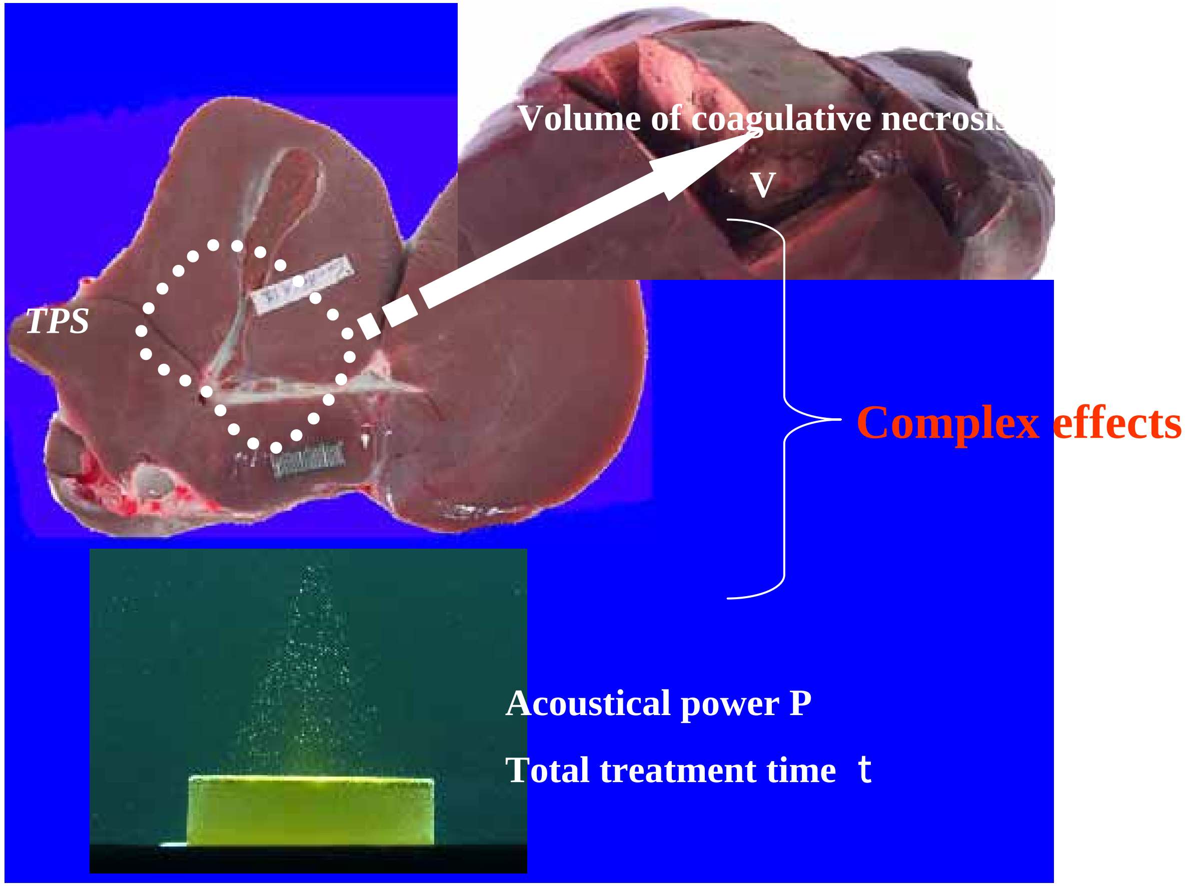


Table 1. Comparison between AFR and BFR induced by HIFU within tissues

	AFR	BFR
Definition	Space contained within the surface defined by −3 dB peak compressional acoustic pressure contours measured around the focus; a concept for energy convergence.	Individual ellipsoid-shaped coagulative necroses induced by a single exposure in tissue. The integral expression of interactions between AFR, acoustic intensity, irradiation depth, exposure time and tissue structure and its functional status; a concept for biological effects
Medium	Free acoustic field (in degassed water)	Various biological tissues *in vitro* and *in vivo*
Shape and volume	Constant	Variable
Correlation with exposure time	No correlation	Positive correlation
Detection mode	Measurable using recognized acoustic techniques	B-mode US scanner, MRI, CT, bare eye inspection, and histopathological evaluation
Significance	Important factor in the formation of BFR	Basic unit for tumor ablation

The Dose for the Use of HIFU in the Extracorporeal Ablation of Tumour: Energy-Efficiency Factor (EEF)

How can we evaluate the therapeutic dose of ablation tumour with HIFU?



Volume of coagulative necrosis

V

Complex effects

Acoustical power P

Total treatment time t

Energy-Efficiency Factor (EEF) may be understood as the energy in joules required to produce coagulative necrosis per cube millimeter in tissue with HIFU.

$$EEF = \frac{\eta \, \mathrm{Pt}}{V} \quad (\mathrm{J/mm^3})$$

Where η ——focusing coefficient of HIFU transducer, which reflects the focusing ability to ultrasound beams of HIFU transducer.

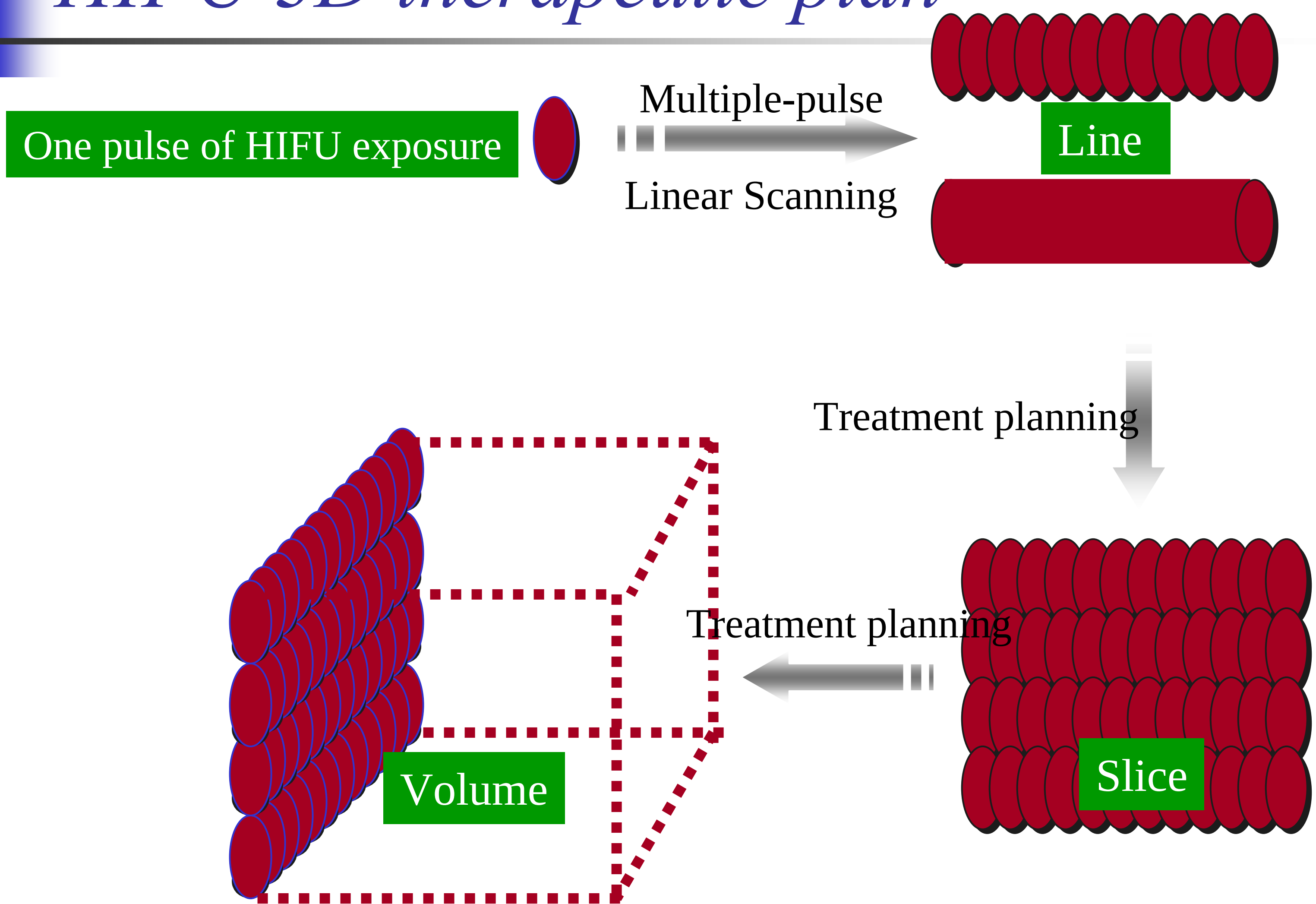
P——Acoustic output power(W).

t ——Total treatment time (s).

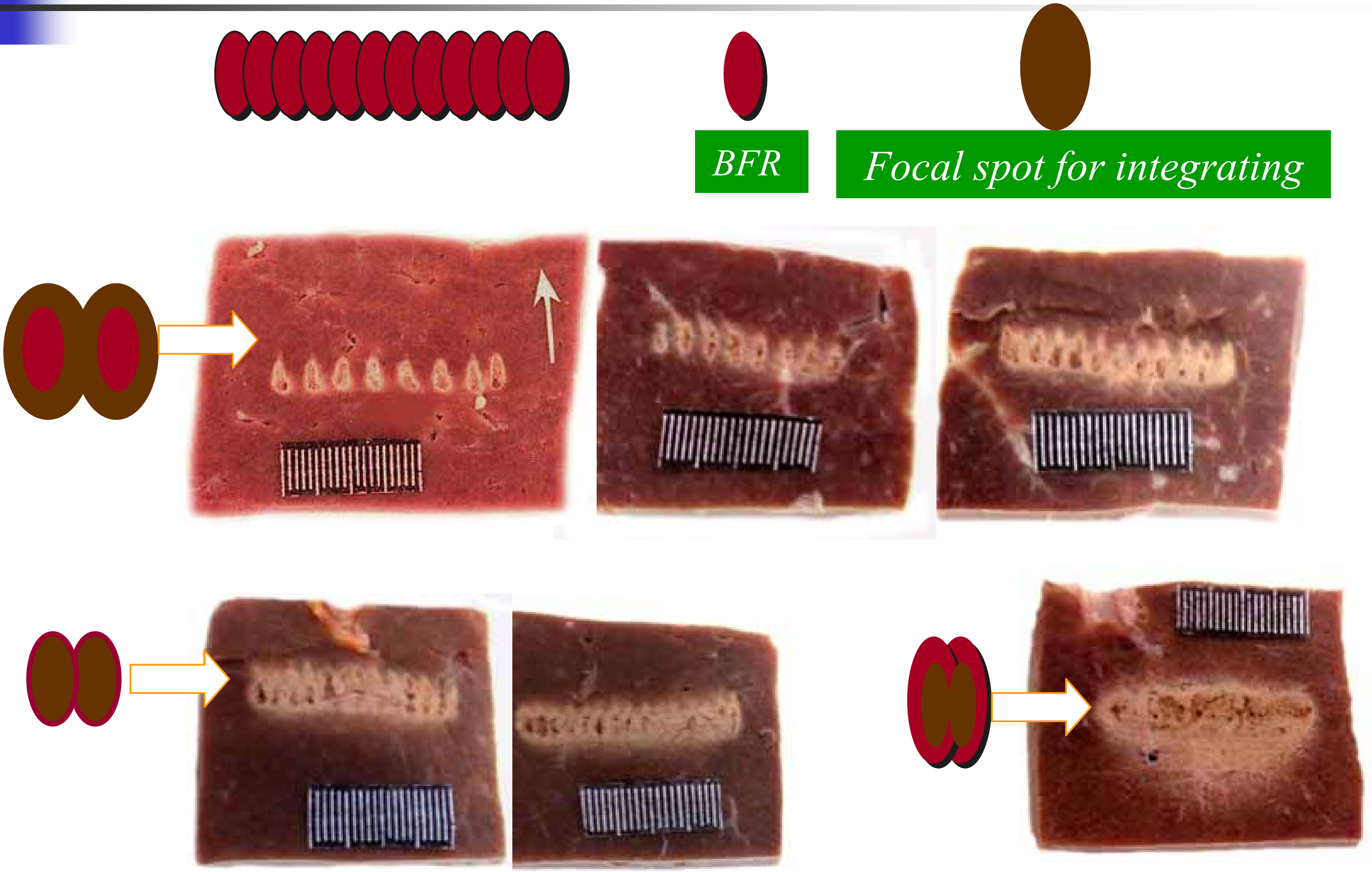
V——Ablated volume (mm^3).

Wang ZB et al. ISTU 2 . 2002;8:14

HIFU 3D therapeutic plan



Line lesion formed inside ox liver using multiple pulse



Line lesion formed inside ox liver using linear scanning

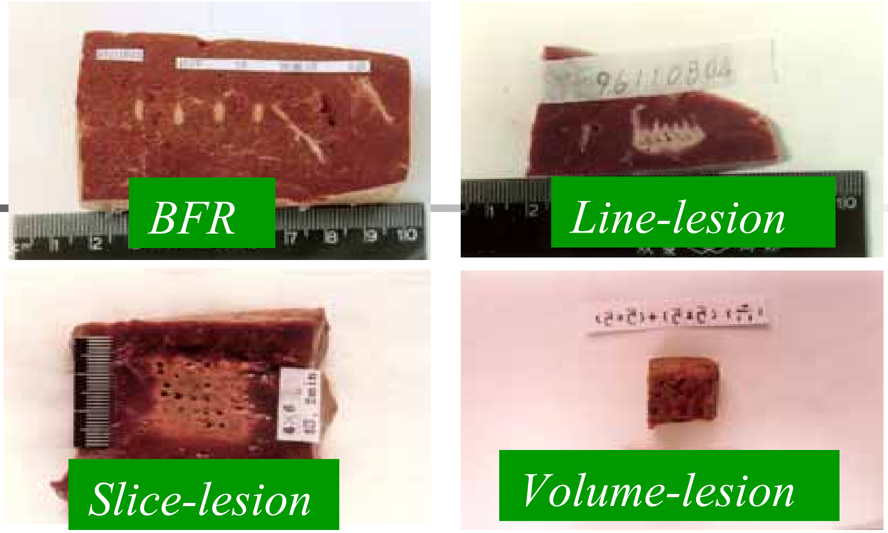
BFR

I=16300W/cm^2
V=2mm/s N=2

I=16300W/cm^2
V=3mm/s N=1

I=16300W/cm^2
V=7mm/s N=1

I=16300W/cm^2
V=6mm/s N=1



BFR, line lesion, slice lesion and volume lesion induced in ox live using multiple pulse

Line lesion, slice lesion and volume lesion induced in ox liver using linear scanning

For one transducer, EEF needed to form line lesion at different depth, slice lesion and volume lesion inside ox liver in vitro with HIFU.

	***EEF*(J/mm^3)**		
	Exposure Depth (mm)	**Multiple pulse**	**Linear scanning**
Line	**20mm**	**14.36±6.55**	**8.41±4.77**
	30mm	**17.31±6.34**	**10.83±5.65**
	40mm	**18.73±6.63**	**11.96±5.17**
	50mm	**23.33±5.77**	
Sclice	**(starting exposure depth 40mm)**		**2.71±0.85**
Volume	**(starting exposure depth 40mm)**		**1.73±0.39**

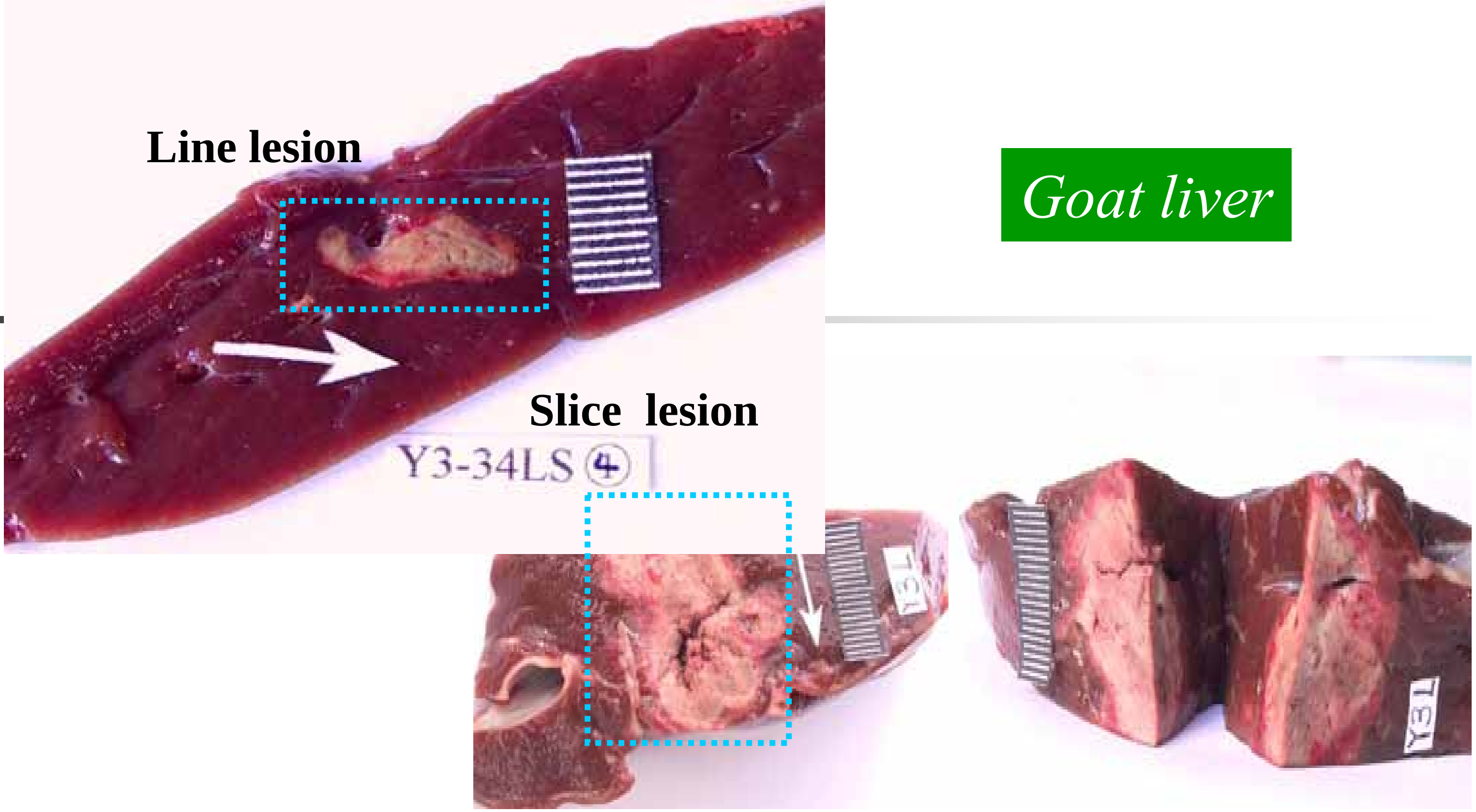
$$EEF_{\text{Lines}} > EEF_{\text{Slices}} > EEF_{\text{Volume}}\,.$$

$$EEF_{\text{Slices}} \neq EEF_{\text{Line1}} + EEF_{\text{Line2}} + EEF_{\text{Line3}} + \cdots$$

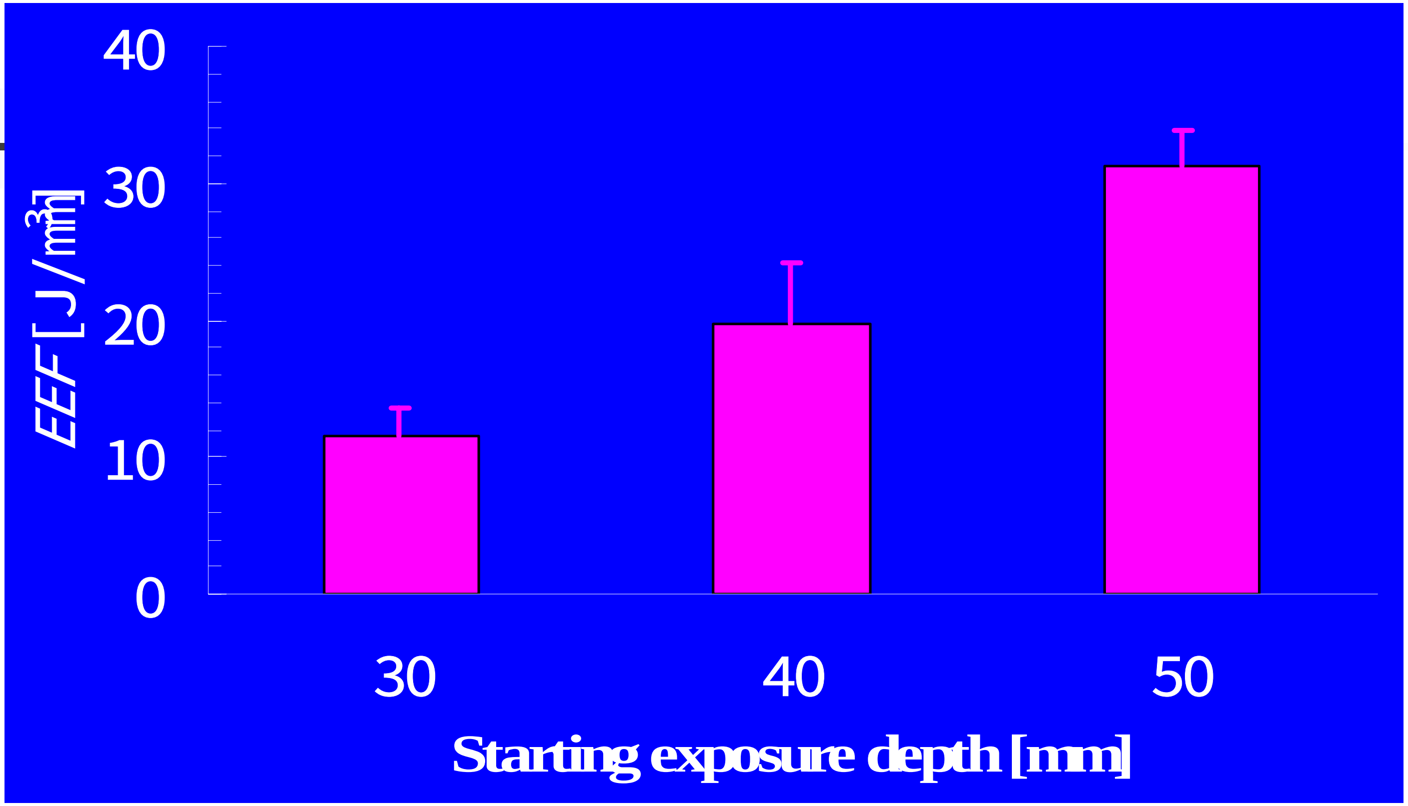
$$EEF_{\text{Volume}} \neq EEF_{\text{Slice1}} + EEF_{\text{Slice2}} + EEF_{\text{Slice3}} + \cdots$$

Dynamic Acoustic Environment in Tissue

Goat liver

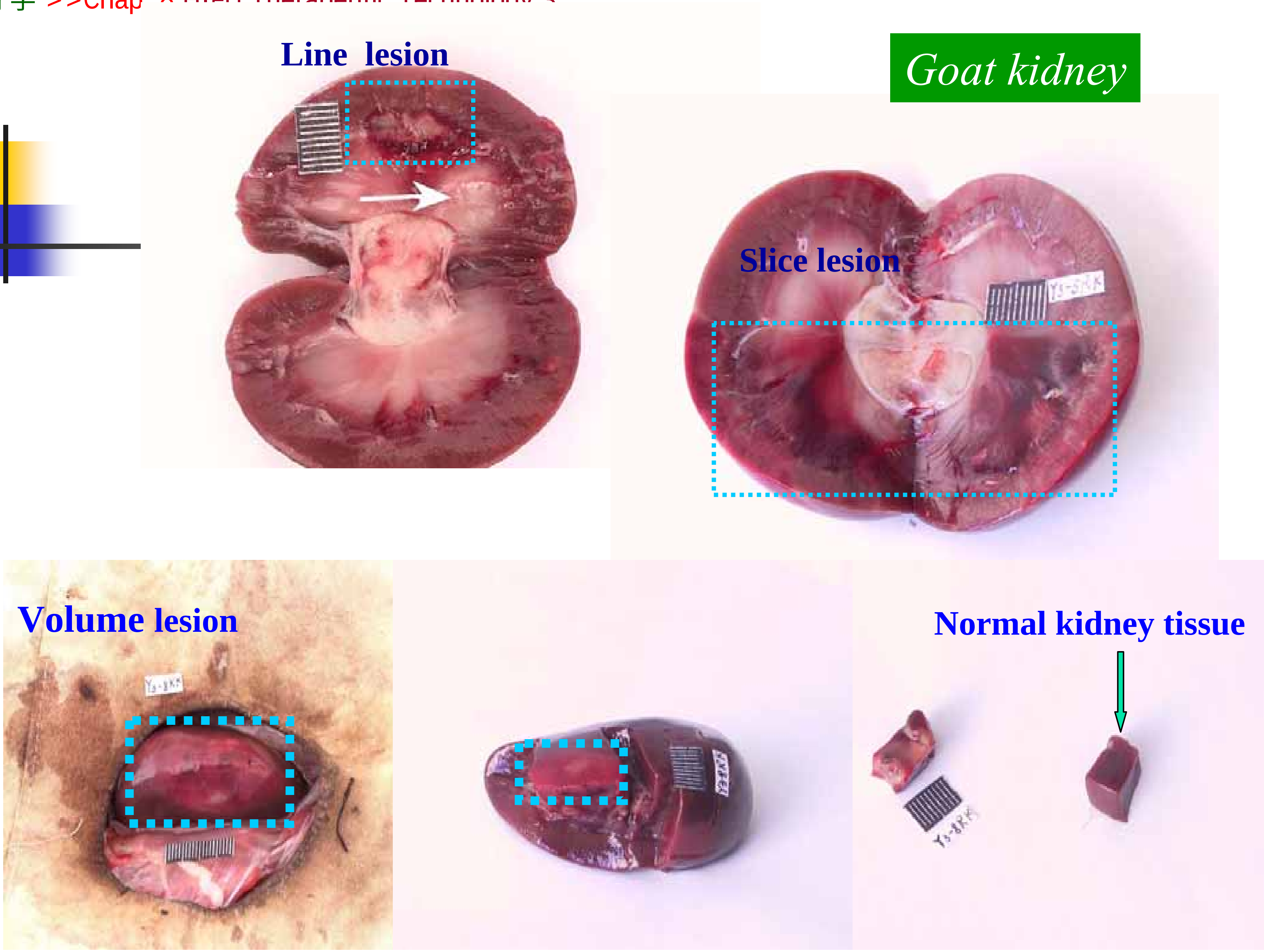

Line lesion
Slice lesion
Y3-34LS ④
Y3L
Y3L

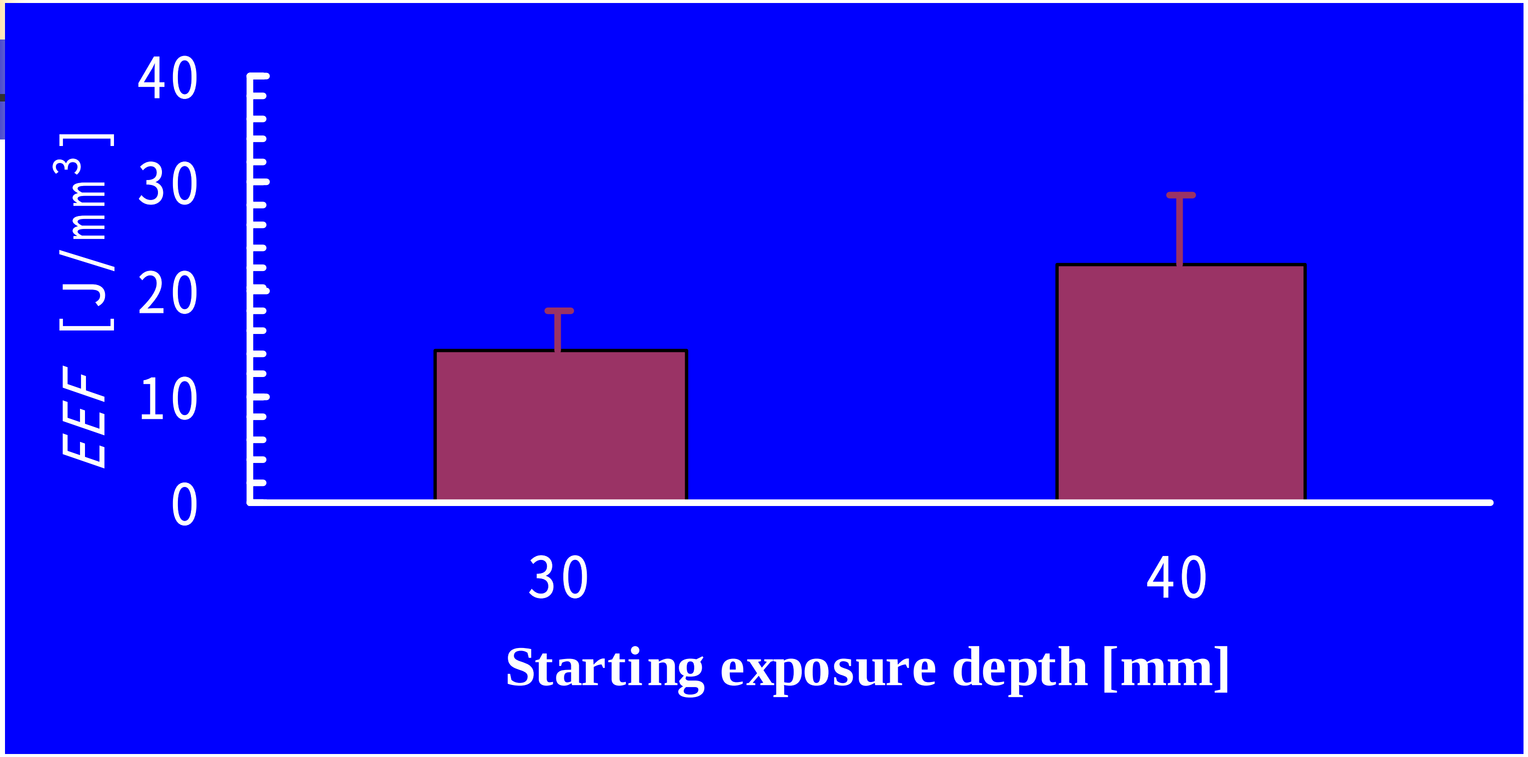

Normal liver tissue
Volume lesion



For one transducer, *EEF* needed to form volume lesion at different starting exposure depth in goat liver *in vivo* with HIFU.

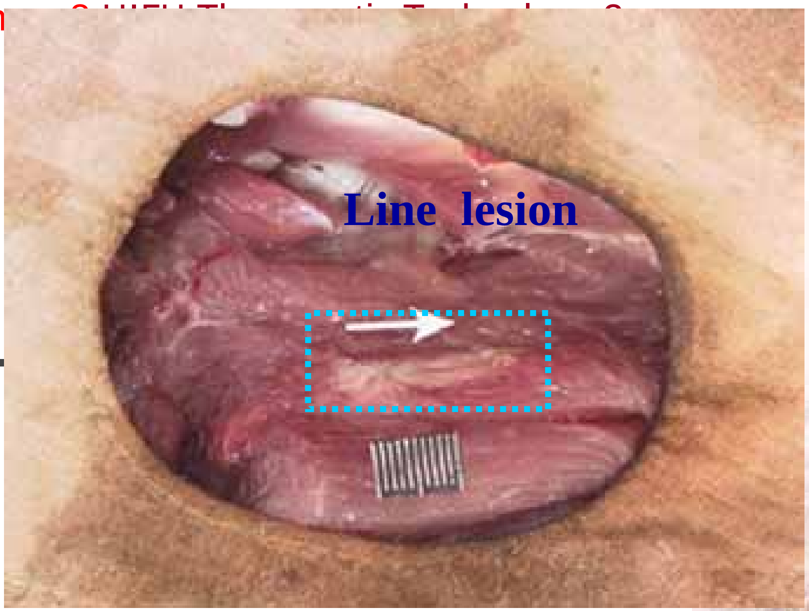
Goat kidney


Line lesion
Slice lesion
Volume lesion
Normal kidney tissue



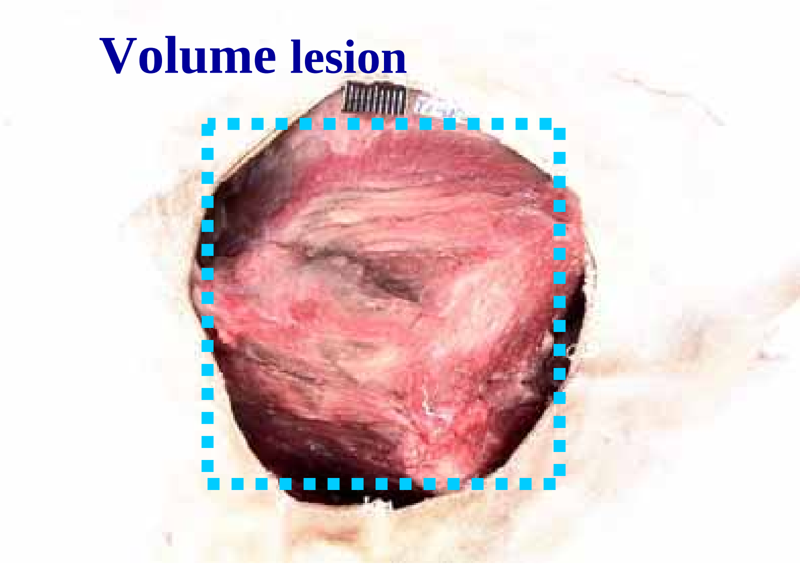
For one transducer, *EEF* needed to form volume lesion at different starting exposure depth in goat kidney *in vivo* with HIFU.

Goat muscle



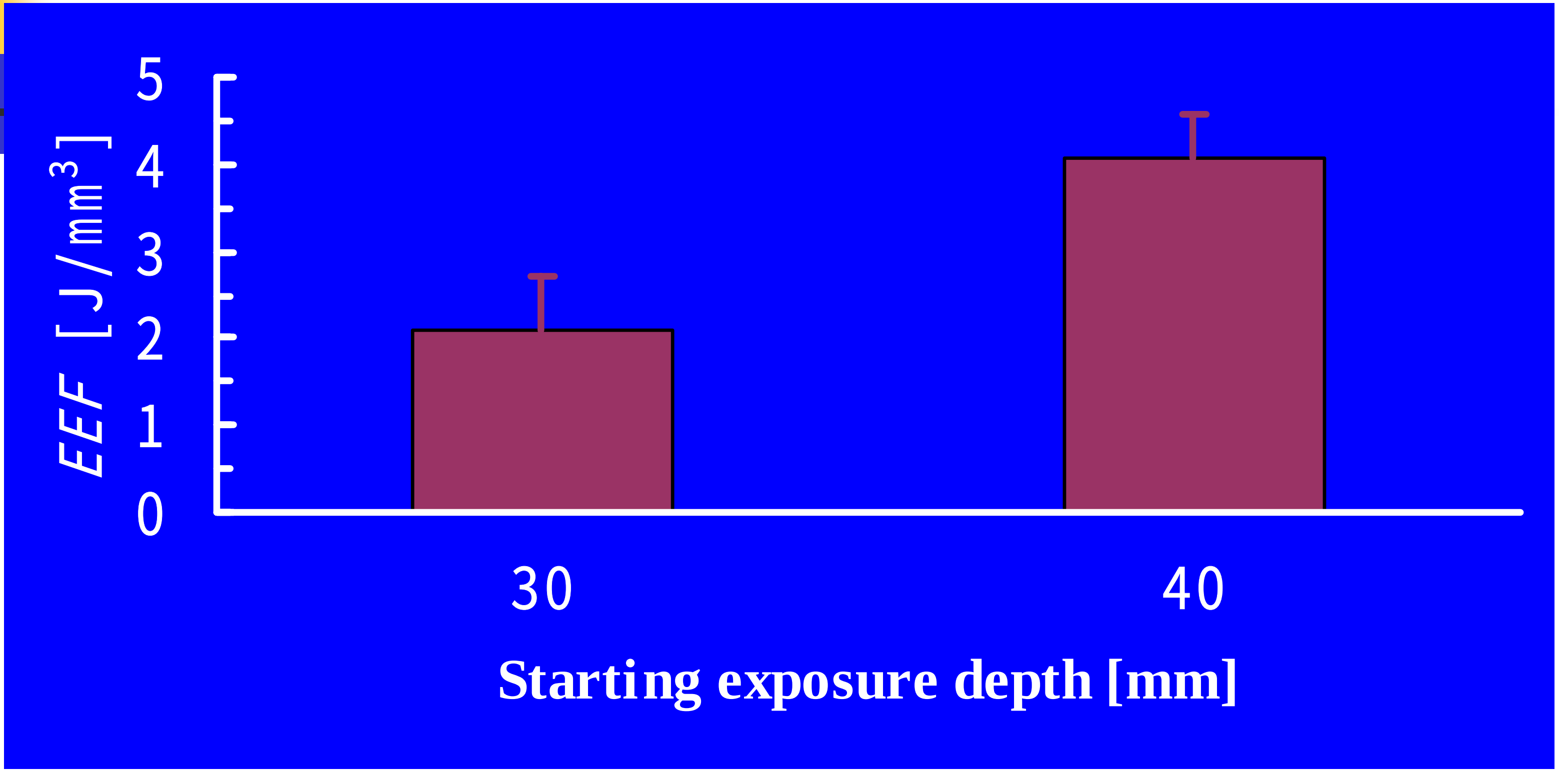
Line lesion

Slice lesion

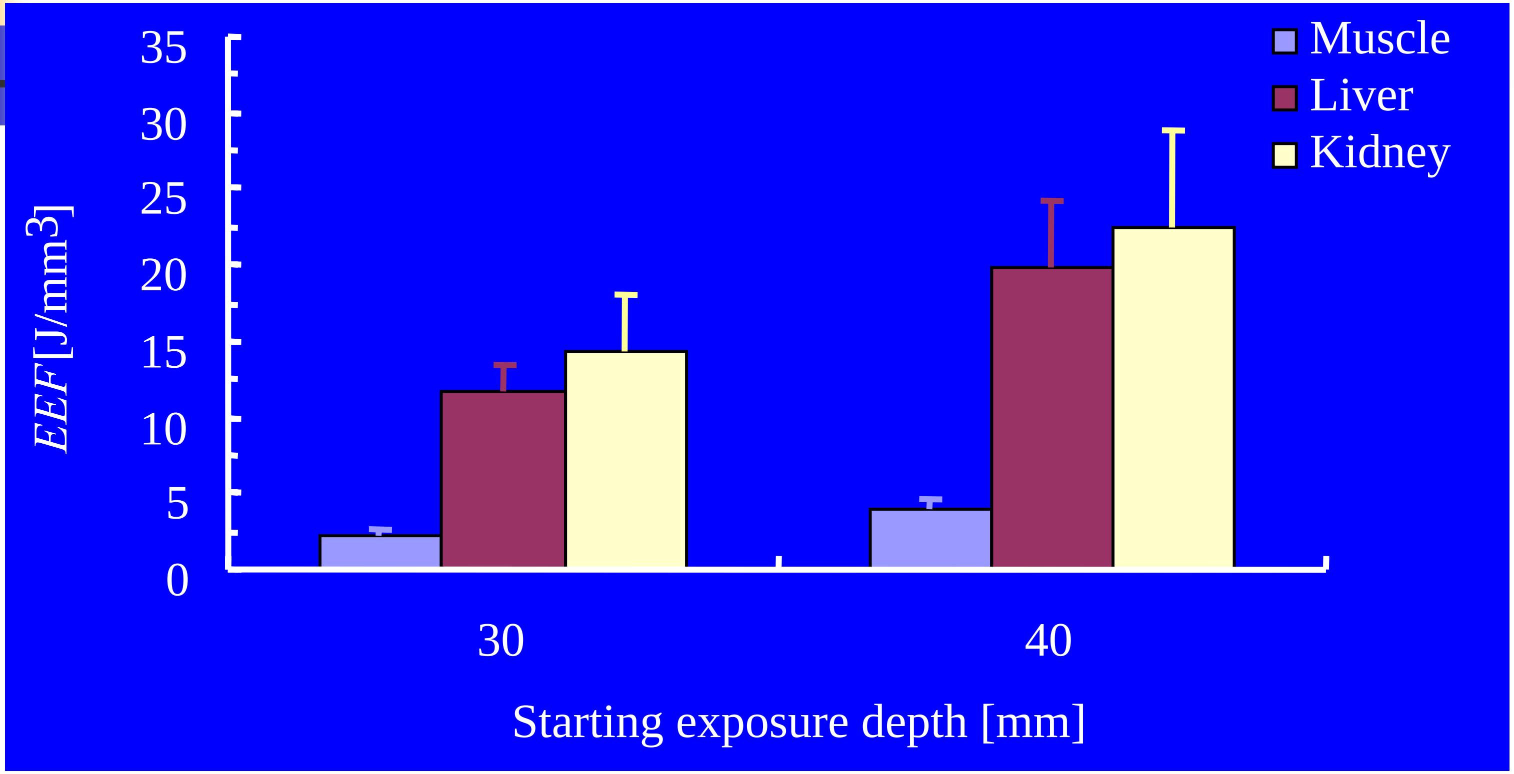


Volume lesion

Normal muscle tissue



For one transducer, *EEF* needed to form volume lesion at different starting exposure depth in goat muscle *in vivo* with HIFU.

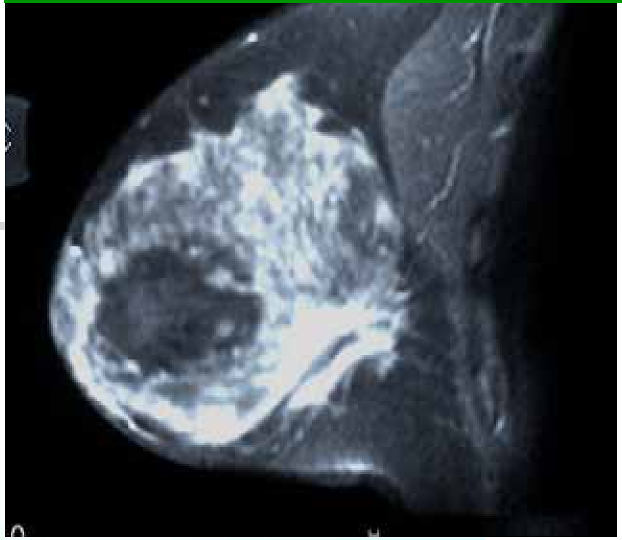


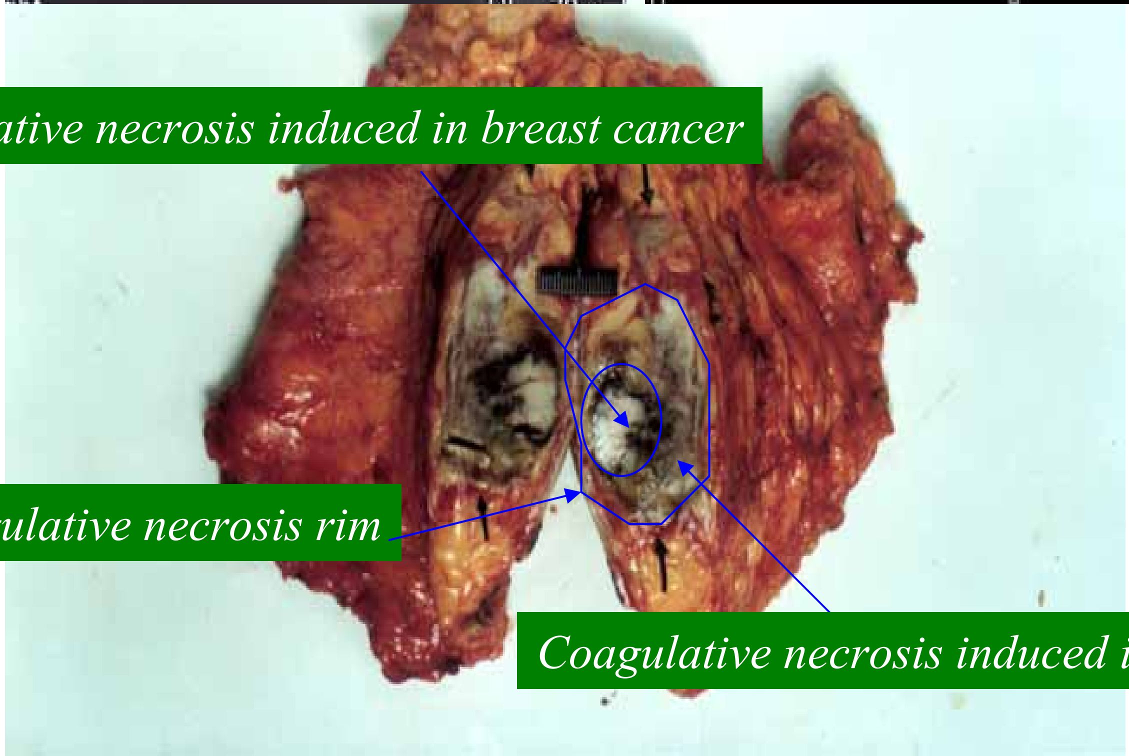
For one transducer, *EEF* comparison for ablation of goat liver, kidney and muscle tissue *in vivo* with HIFU.

Breast cancer

T1W MRI imaging Before HIFU

T1W MRI imaging 1 month After HIFU

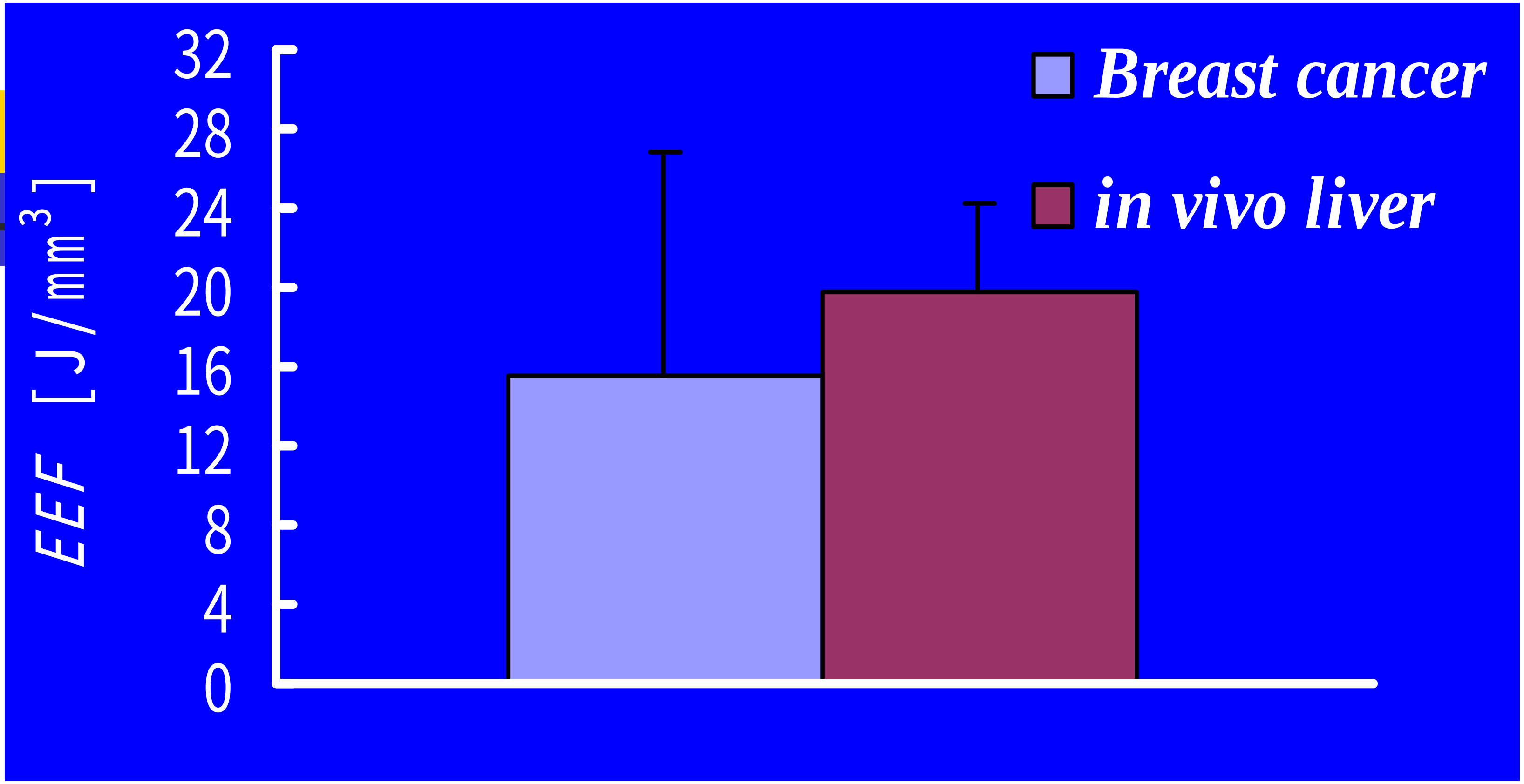




Coagulative necrosis induced in breast cancer

Coagulative necrosis rim

Coagulative necrosis induced in breast tissue



EEF for treating breast cancer and forming volume-shaped lesion inside goat liver at starting exposure depth 40mm with HIFU.

Application of EEF: To predict in advance the total treatment time for HIFU ablation of tumour in clinic in terms of experimental data.

The experimental results showed *EEF* was 31.3J/mm^3 for forming volume lesion at starting exposure depth 5cm in goat liver with HIFU. So we can evaluate the total treatment time needed for extra-corporeal ablation tumour of (2cm)^3 at a starting exposure depth of 5cm with HIFU.

$$\boxed{EEF = \frac{\eta \mathrm{Pt}}{V}} \quad (\mathrm{J/mm^3})$$

Where *EEF* is 31.3J/mm^3.η is 0.7, which reflects the focusing ability of ultrasound beams of HIFU transducer, Acoustic power P used in clinic is 200W , volume of tumour V is 8000mm^3.

Therefore total treatment time needed for ablating a tumour of (2cm)^3 with HIFU is 30min.

Study on AET (Acoustic Environment in Tissue) and RAET (Remolding Acoustic Environment in Tissue) of HIFU treatment tumors

Challenge

- Tumors in deeper
- Large tumors
- Hepatic tumors shielded by ribs in HIFU beam pathway

Inspiration

- Difference of BFR and EEF between liver, kidney and muscle
- HIFU treatment bone tumour
- TAE

Acoustic Environment in Tissue

AET (Acoustic Environment in Tissue, AET) may be understood as the biological structure, function and acoustic properties in tissue before, during and after being treated with HIFU.

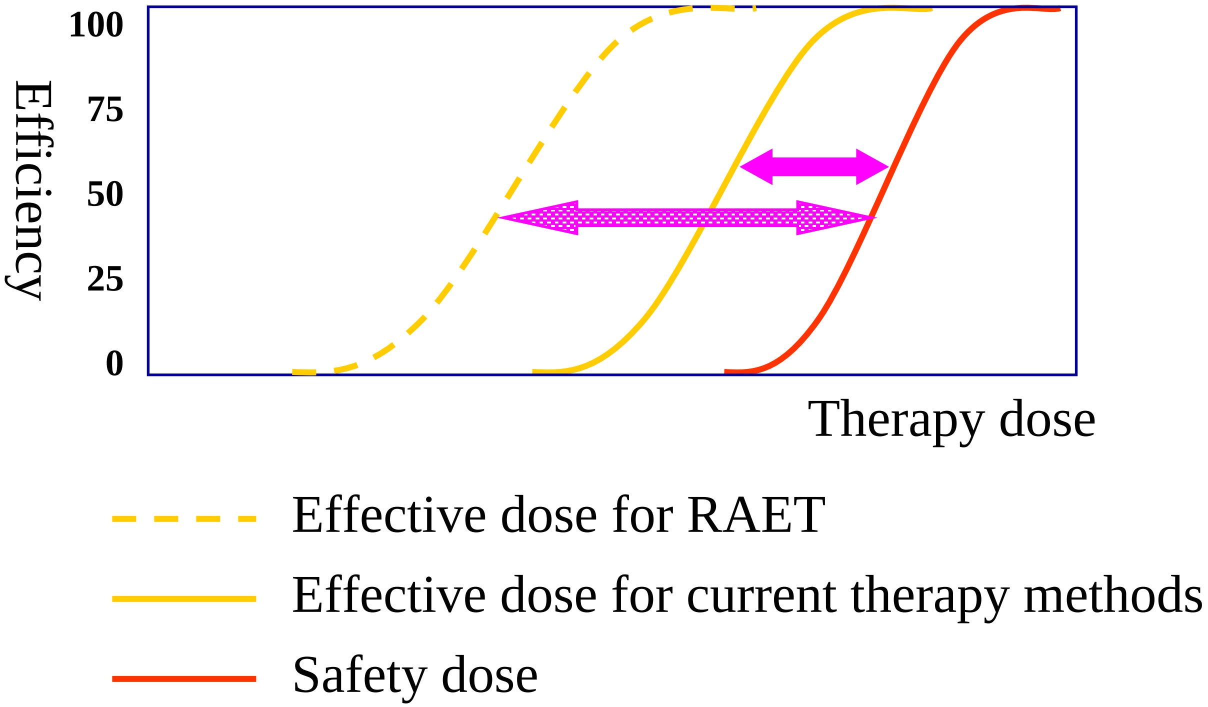
The favorable AET are: first, the target tissue has as much as possible energy deposition comparing to that of surrounding tissue; second, there is a reflecting interface behind the target region.

Wang Zhibiao et al. 3rd International Symposium on Therapeutic Ultrasound, 22-25 June 2003, Lyon, France, P68

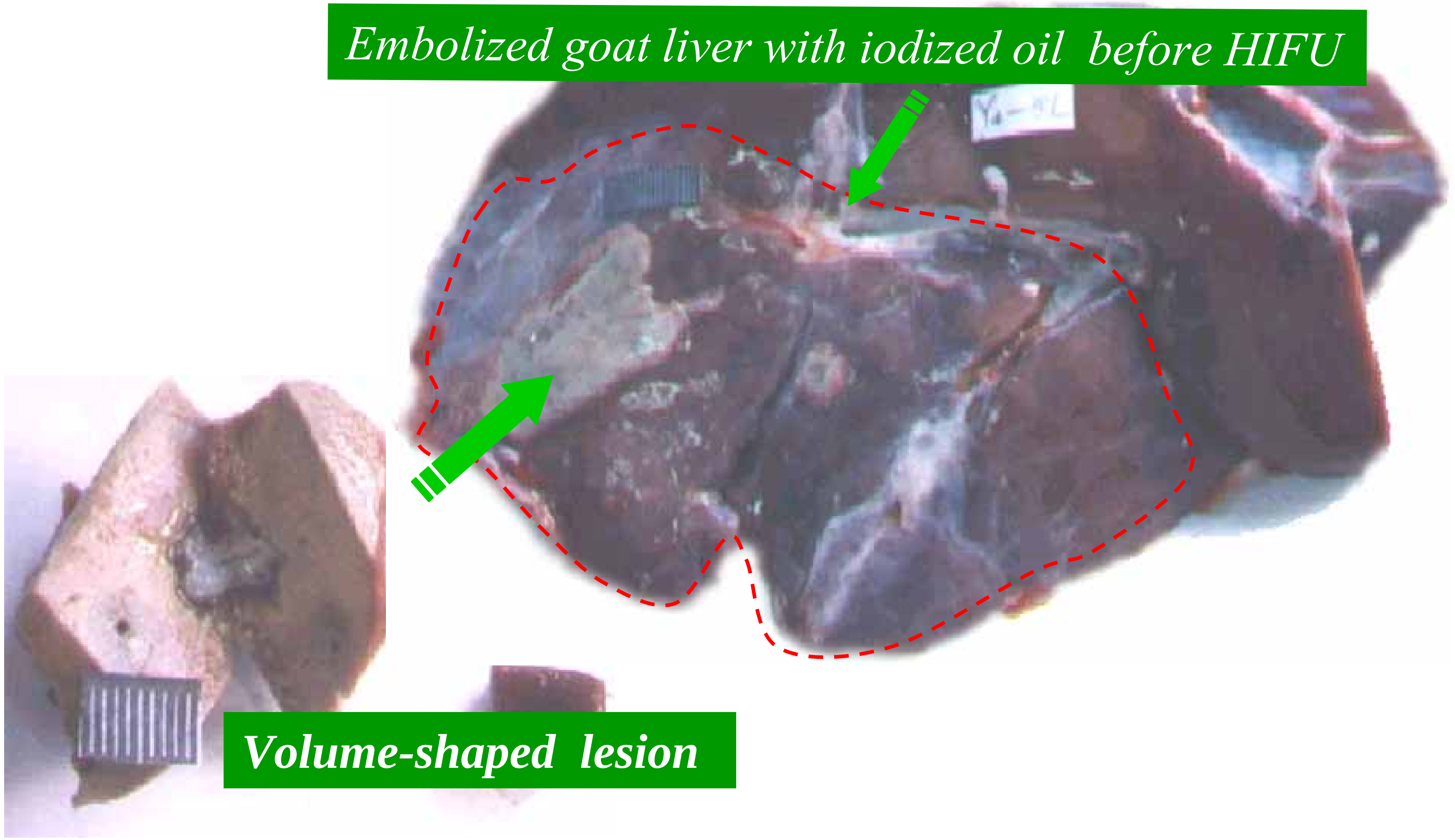
Remolding Acoustic Environment in Tissue

RAET may be understood as developing some approaches to change tissue structure and function for speeding up delivery of ultrasound energy.

Aims


100
75
50
25
0
Efficiency
Therapy dose
- - - Effective dose for RAET
— Effective dose for current therapy methods
— Safety dose

RAET : Embolized goat liver with iodized oil



Embolized goat liver with iodized oil before HIFU

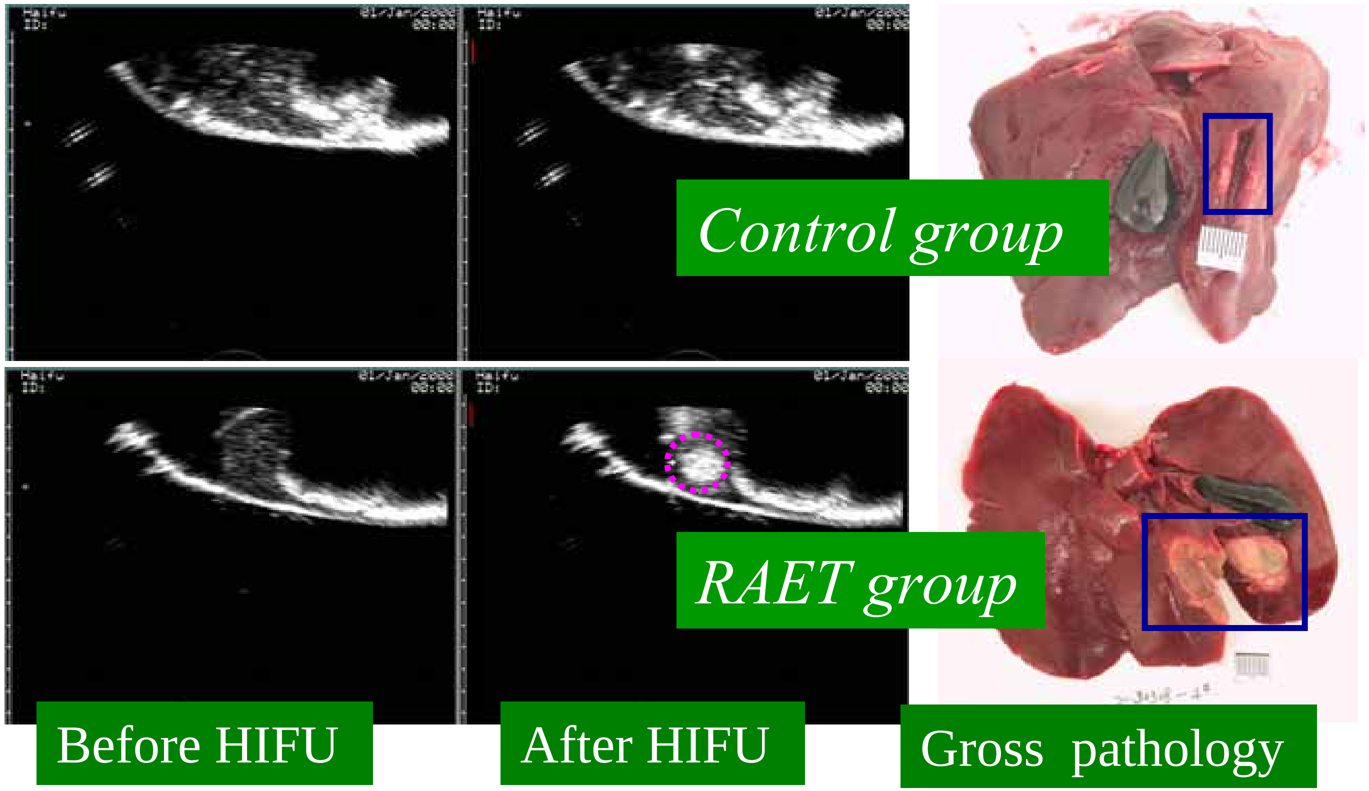
Volume-shaped lesion

*** Embolizated liver with iodized oil vs. Normal $p < 0.05$**

*** Starting irradiation depth 40mm**

Comparison of *EEF* needed between normal and embolized liver with iodized oil ablated by HIFU.

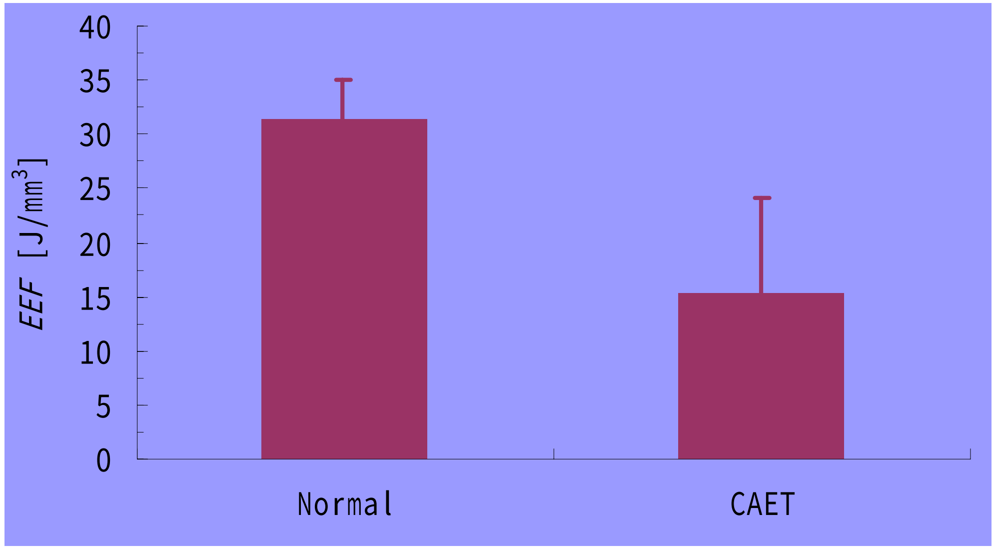
A promising method of RAET: IV injection of Microbubble agents



Goat liver

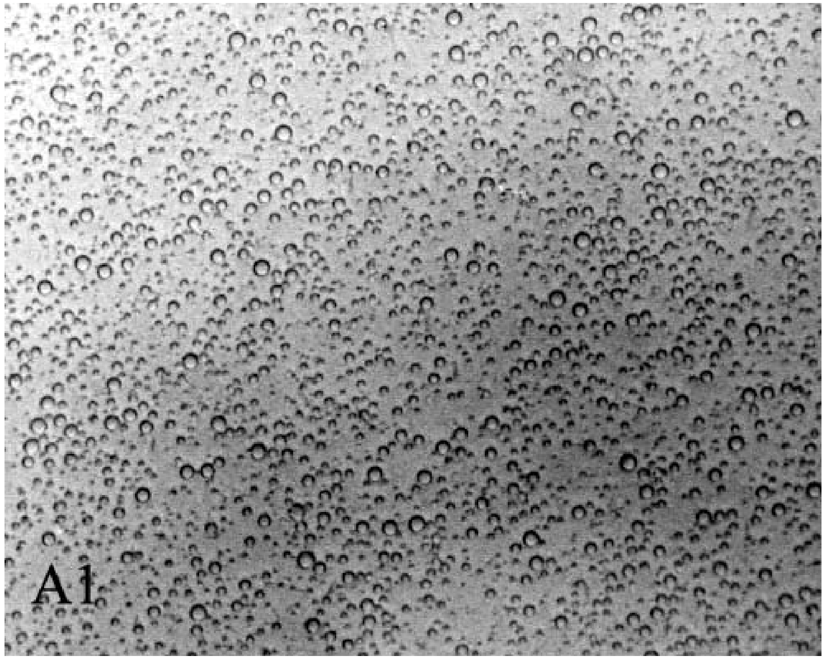
9

IV injection of microbubble agent



Comparison of *EEF* between control and goat liver of RAET ablated by HIFU

RAET : Using phase shift perfluoropentane emulsion (PSPE)



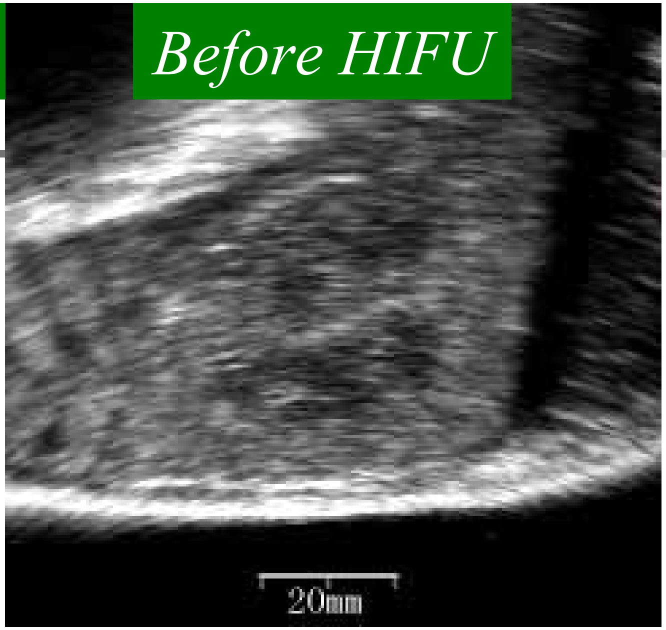
PSPE droplets (4 hours after preparation, diluted 100 times, ×400)

EEF of HIFU ablation control and RAET rabbit liver

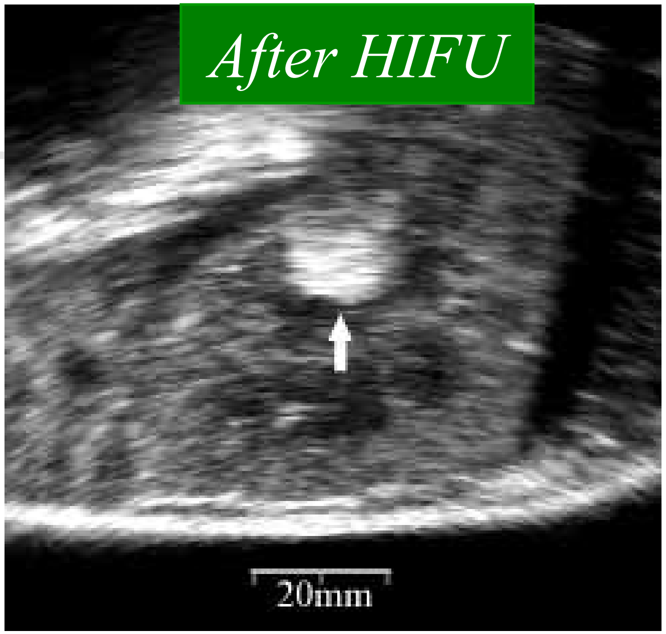
	Control group	RAET group	p
V (mm^3)	219.91	554.18	0.001
EEF (J/mm^3)	5.15	1.35	0.000

HIFU combined with PSPE

Goat kidney

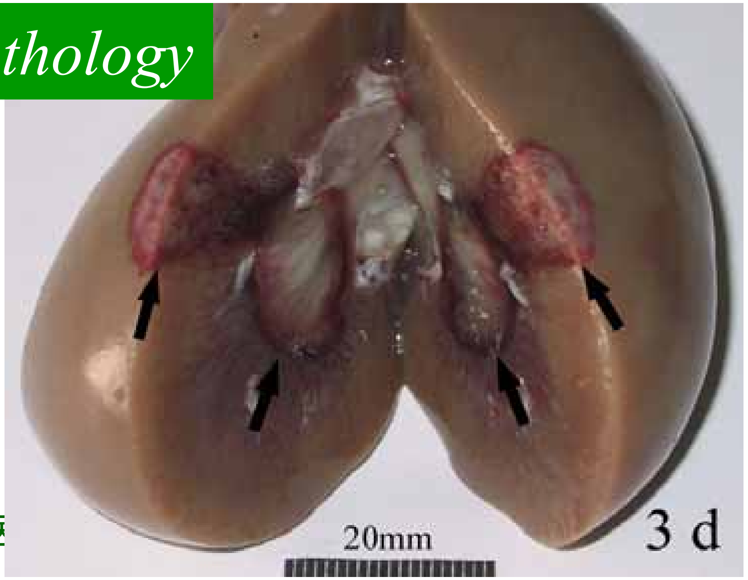


Before HIFU



After HIFU

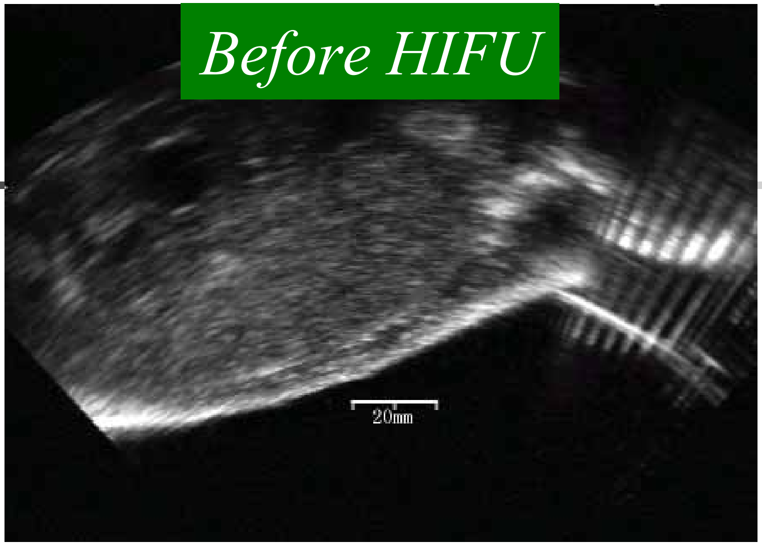
Gross pathology

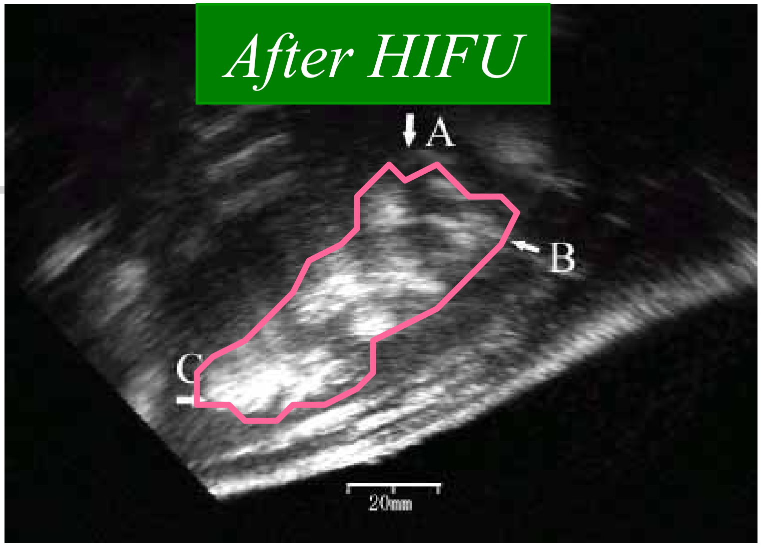


EEF of HIFU ablation control and RAET goat kidney

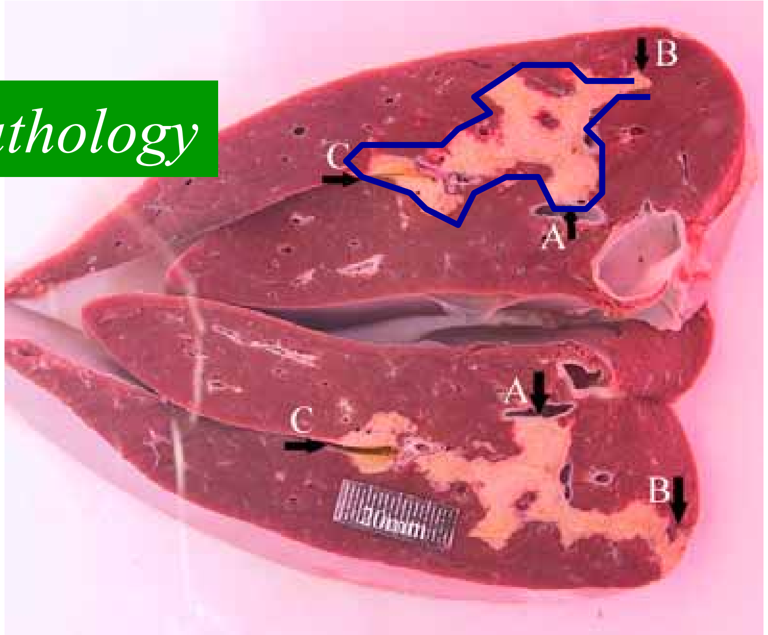
Group	N	EEF (J/mm^3)	*P*
Control	15	169.04	0.000
RAET	15	8.74	

Goat Liver HIFU combined with PSPE

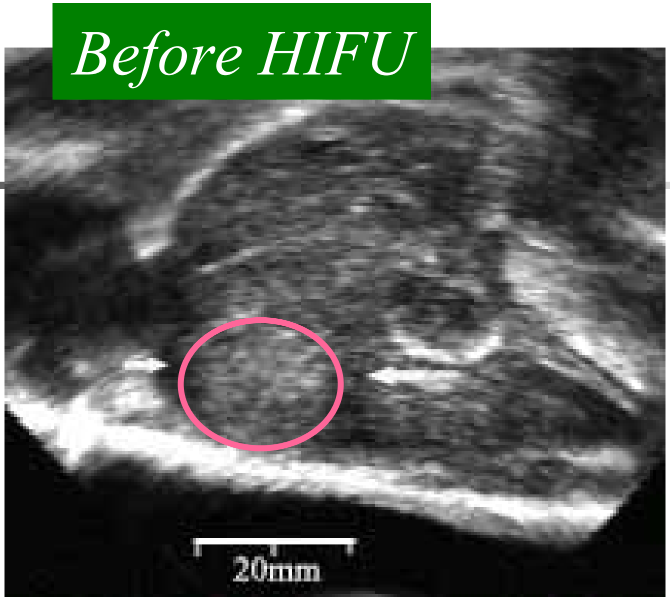

Before HIFU

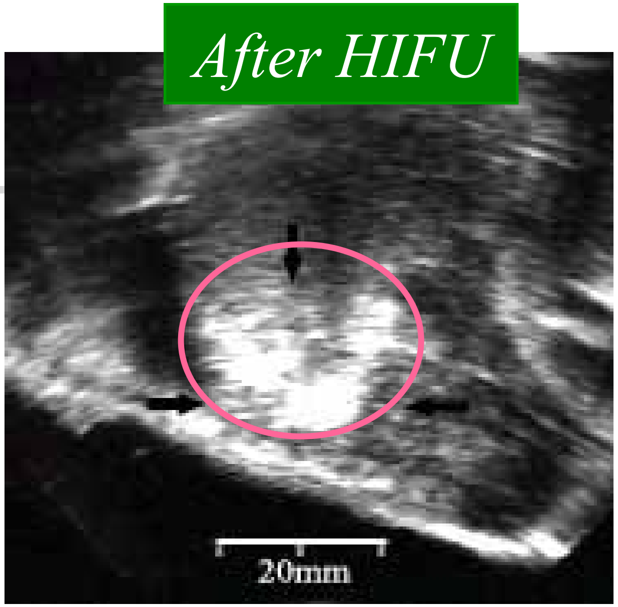

After HIFU

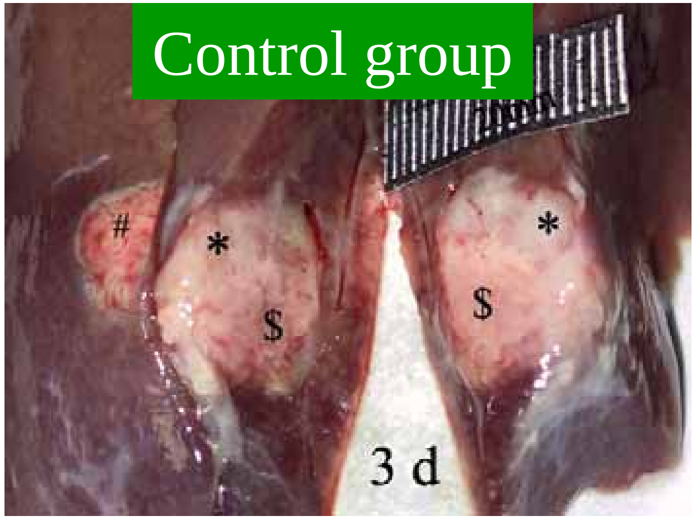
Gross pathology

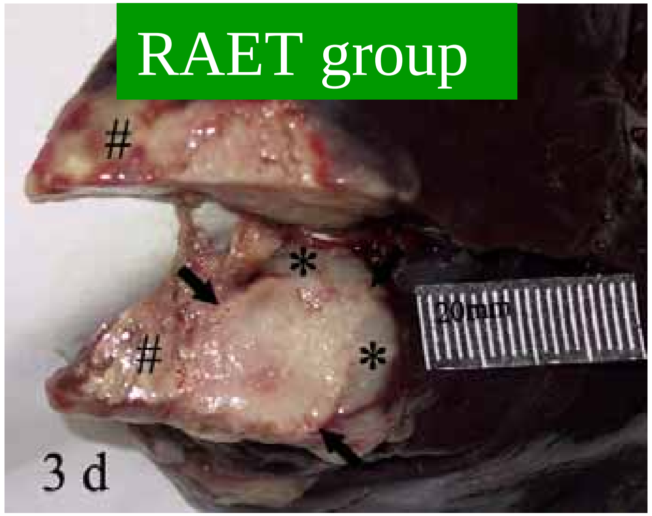


Rabbit VX2 liver tumour *HIFU combined with PSPE*


Before HIFU

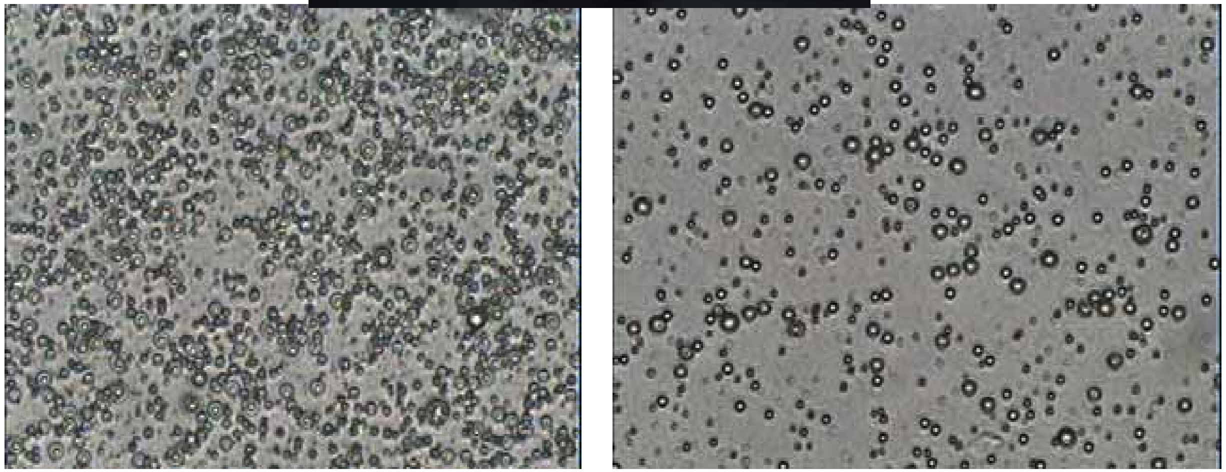

After HIFU


Control group


RAET group

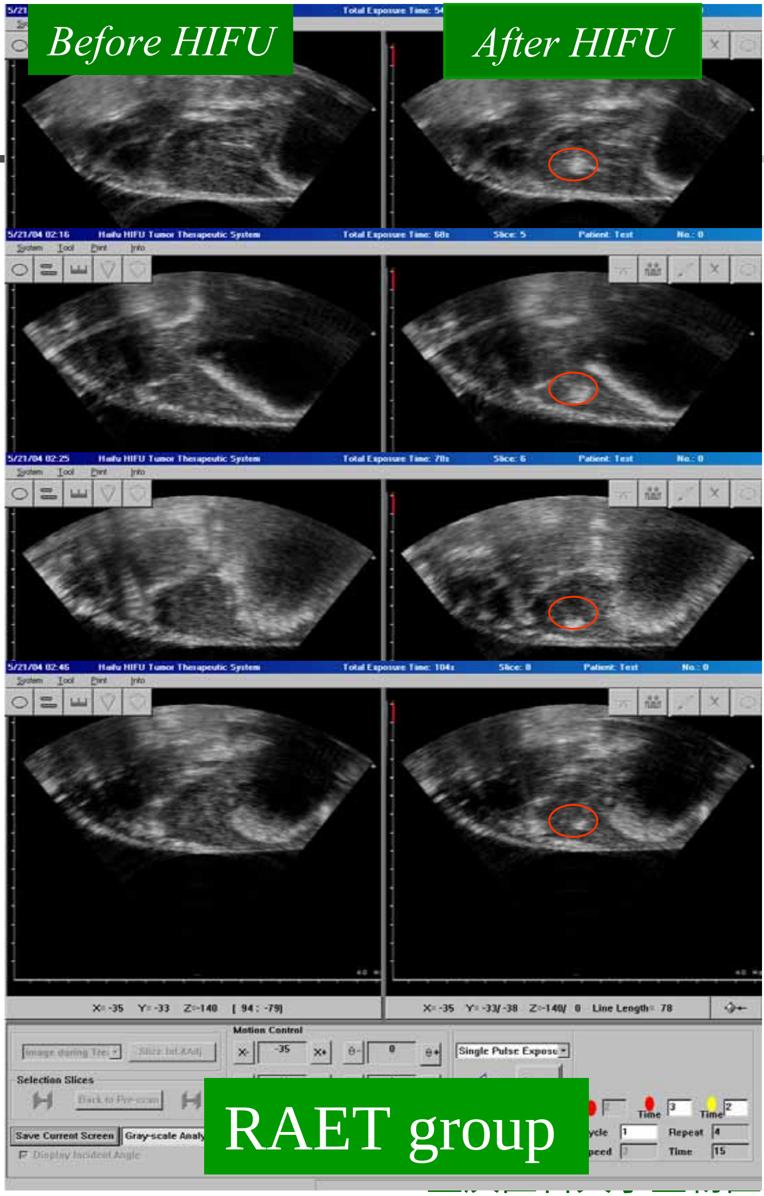
RAET : Using HL-2

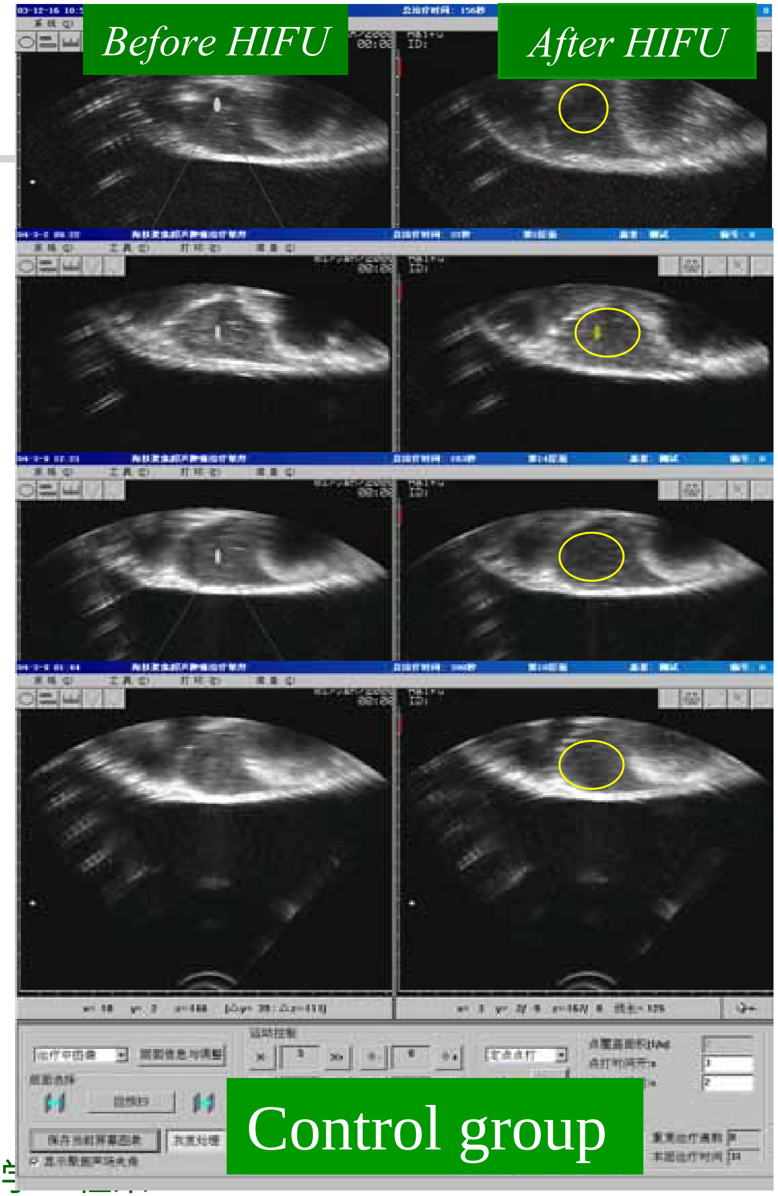
HL-2



The light microscopic image of HL-2（×400), 10 fold diluted (Left) and 100 fold diluted (Right)

Rabbit Liver HIFU combined with HL-2





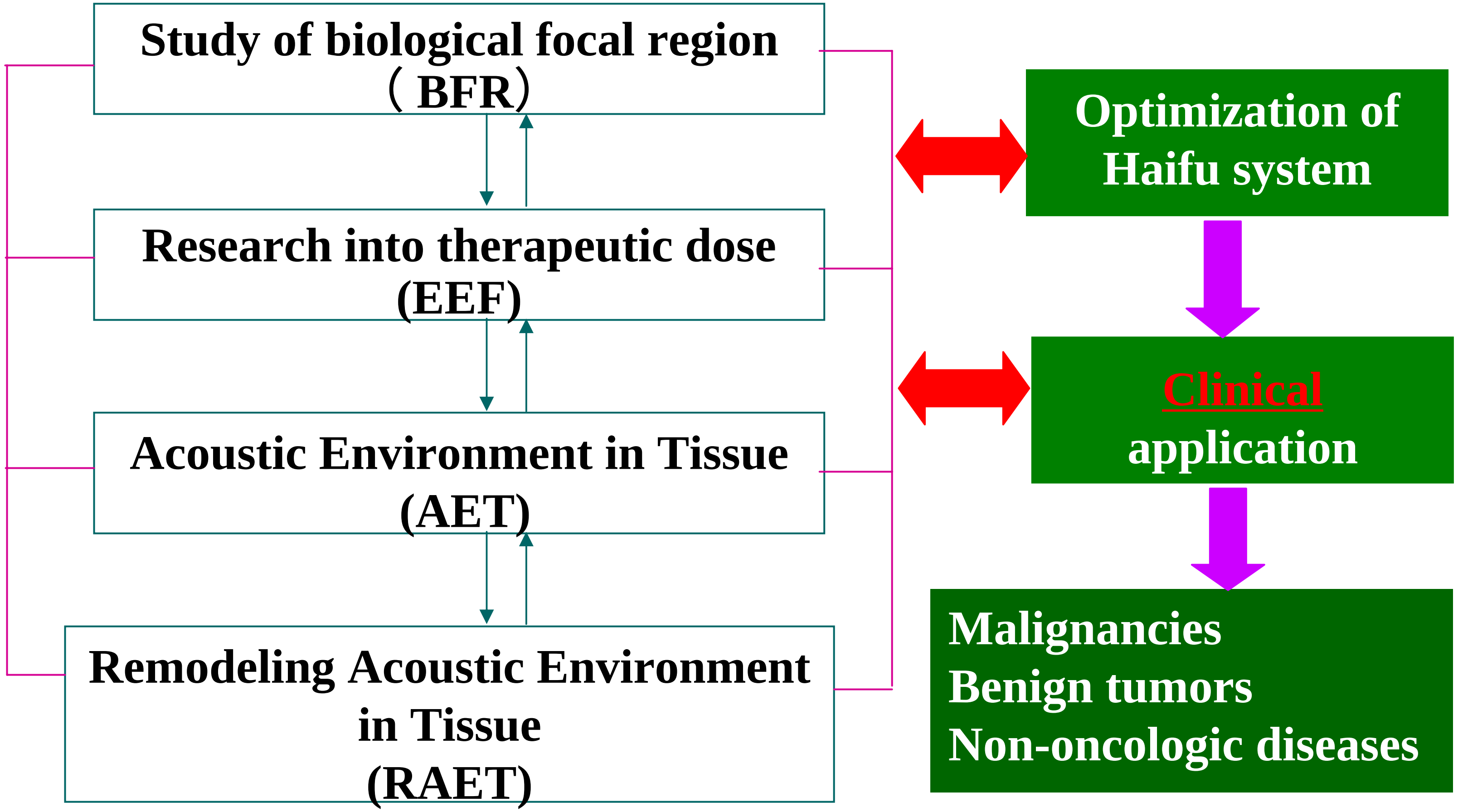
EEF of HIFU ablation control and RAET rabbit liver

分 组	n	EEF (mean±s)
HL-2	48	7.16±1.38
NS	15	31.05±2.68
P		<0.001

Unknown

- Mechanism
- Effect of type of microbubble agents on improvement of treatment efficiency
- Optimal treatment protocol for HIFU combination with microbubble agents
- Toxicity of microbubble agents exposed to HIFU
- -----

The General Scheme for the Research of HIFU Technologies



Study of biological focal region （BFR）

Research into therapeutic dose (EEF)

Acoustic Environment in Tissue (AET)

Remodeling Acoustic Environment in Tissue (RAET)

Optimization of Haifu system

Clinical application

Malignancies
Benign tumors
Non-oncologic diseases

Clinical application of HIFU

Malignancies

- Liver cancer
- Breast cancer
- Malignant bone tumors
- Renal cancer
- Soft tissue tumors
- Pancreatic cancer
- Melanoma
- Lymphomas

Benign tumors

- Mammary fibroma
- Hysteromyoma
- Lipoma
- Fibroma
- Fibromatosis

Non-oncologic diseases

- White lesions of vulva
- condyloma acuminata
- Cervicitis

Future

In Feb. 2004, the US congress gathered 30 top scientists of the world to discuss the frontier sciences, therapeutic ultrasound (HIFU technology) was discussed for the first time.

Paper published in Nature on 05

- Samir Mitragotri . Innovation: Healing sound: the use of ultrasound in drug delivery and other therapeutic applications. Nature Reviews Drug Discovery 4, 255-260 (01 Mar 2005)
- James E. Kennedy. Innovation: High-intensity focused ultrasound in the treatment of solid tumours .Nature Reviews Cancer 5, 321-327 (01 Apr 2005)
- Christian Chaussy, Stefan Thüroff, Xavier Rebillard, Albert Gelet. Technology Insight: high-intensity focused ultrasound for urologic cancers. Nature Clinical Practice Urology 2, 191-198 (01 Apr 2005)