Present and Future Hyperthermia Technology Evolution

Paul F. Turner CTO

Pyrexar Medical Corporation

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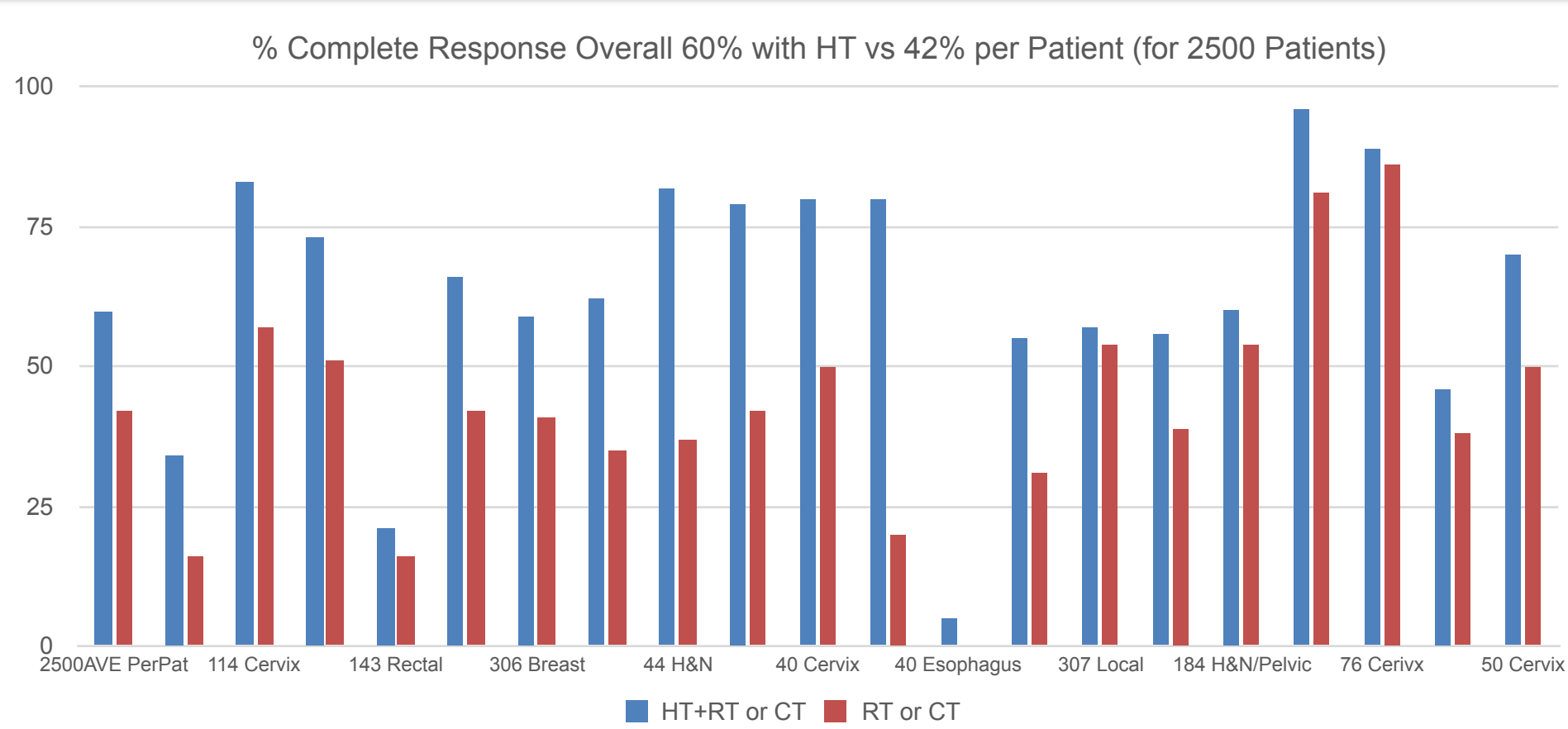
How are we doing?

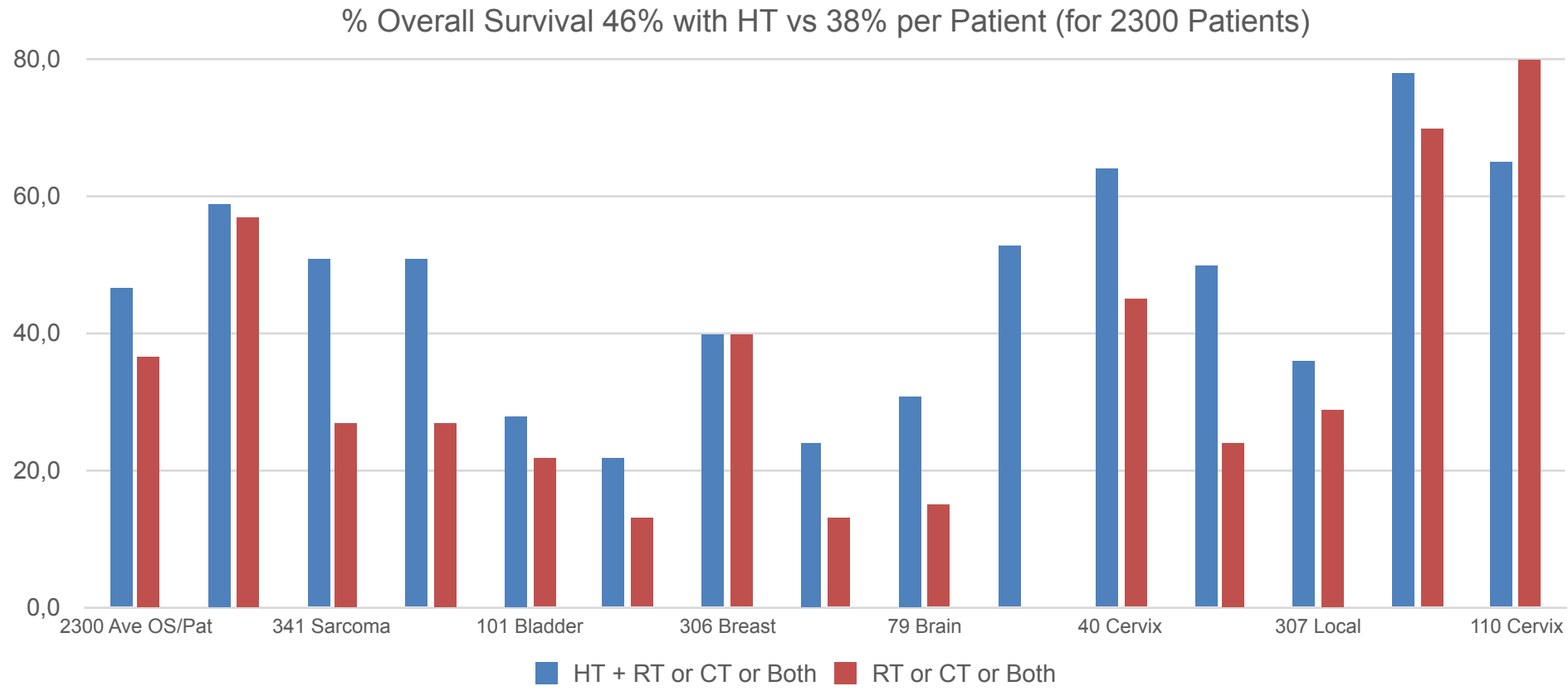
- Reviewed 29 randomized/Phase III studies
- Reviewed criteria as reported
  - Complete response rates
  - Disease Free Survival
  - Overall survival
  - Toxicity Grade III and IV

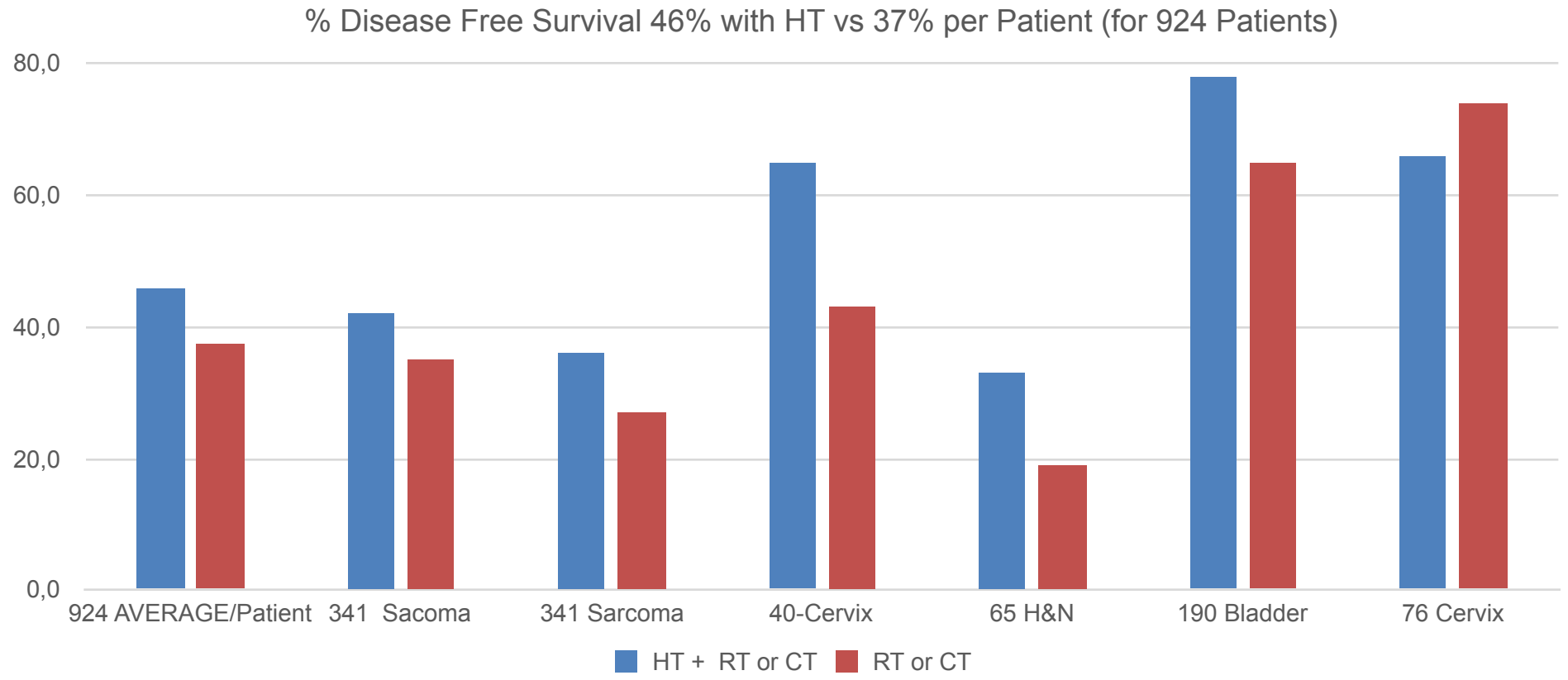
Randomized Studies Reviewed

Author	Site	Pat. #
Issels	S Sarcoma	341
Issels (JAMA)	s Sarcoma	341
Zee	cervical	114
Zee	bladder	101
Zee	rectal	143
Jones	breast	109
Vernon	breast	306
Overgaard	melanoma	128
Colombo	bladder	75
Sneed	brain	79
Valdagni	Head/neck	44
Huilgol	Head/neck	56
Harima	cervical	40

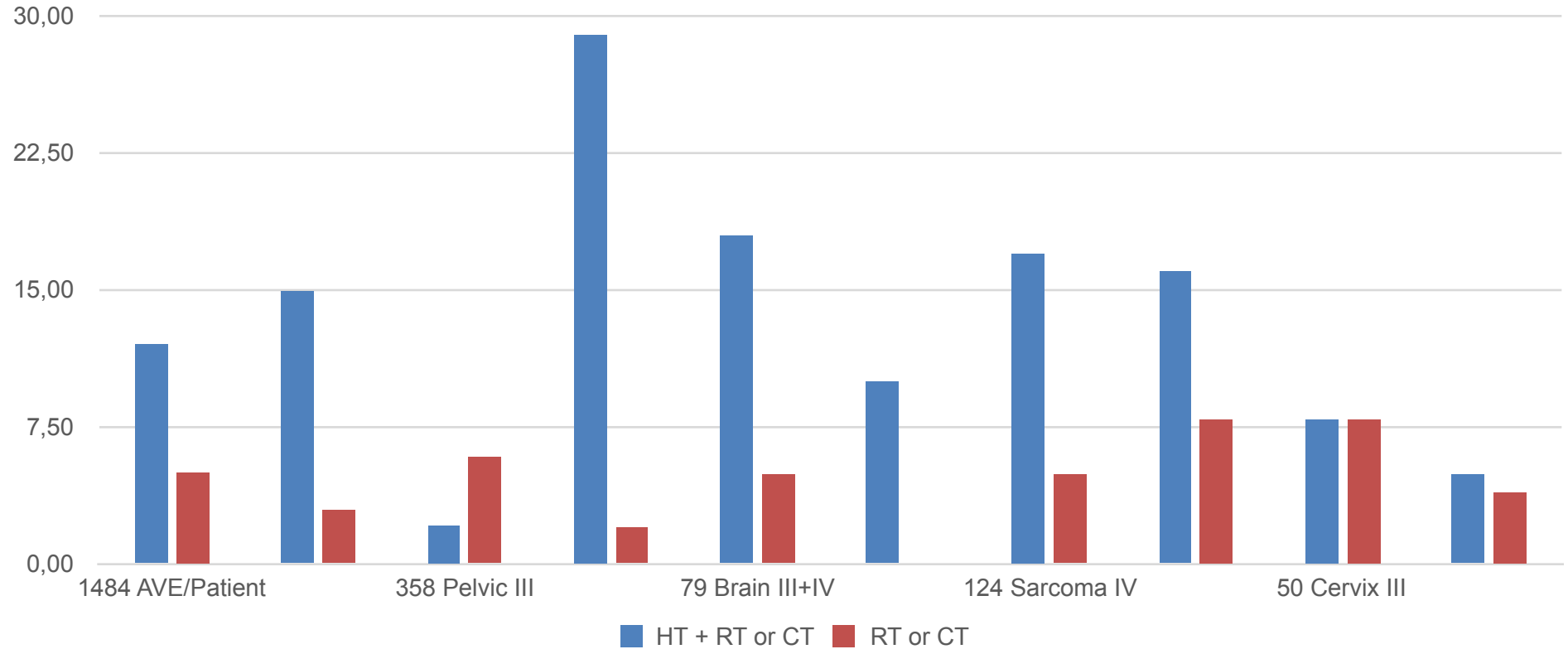
Author	Site	Pat. #
Cornett	S Sarcoma	124
Kitamura	esophagus	66
Sugimachi	esophagus	40
Datta	Head/neck	65
Arends	Bladder	190
Perez	local	307
Perez	Local<3cm	
Emami	H&N/Pelv	184
Hua	nasoph	180
Siwinska	cervical	76
Egawa	VariousSuper	92
Sharma	cervical	50
Vasanthan	cervical	110


% Complete Response Overall 60% with HT vs 42% per Patient (for 2500 Patients)
100
75
50
25
0
2500AVE PerPat
114 Cervix
143 Rectal
306 Breast
44 H&N
40 Cervix
40 Esophagus
307 Local
184 H&N/Pelvic
76 Cerivx
50 Cervix
HT+RT or CT
RT or CT


% Overall Survival 46% with HT vs 38% per Patient (for 2300 Patients)
80,0
60,0
40,0
20,0
0,0
2300 Ave OS/Pat
341 Sarcoma
101 Bladder
306 Breast
79 Brain
40 Cervix
307 Local
110 Cervix
HT + RT or CT or Both
RT or CT or Both


% Disease Free Survival 46% with HT vs 37% per Patient (for 924 Patients)
80,0
60,0
40,0
20,0
0,0
924 AVERAGE/Patient
341 Sacoma
341 Sarcoma
40-Cervix
65 H&N
190 Bladder
76 Cervix
HT + RT or CT
RT or CT

% Toxicity Grade III and IV 9% with HT vs 5% per Patient (for 1484 Patients)



BSD-500, 915MHz, Eight Outputs 0- 60watts or single 400watt output channel, non-metal temperature probes with No MW artifact or interference, Superficial and interstitial applications, CE Mark

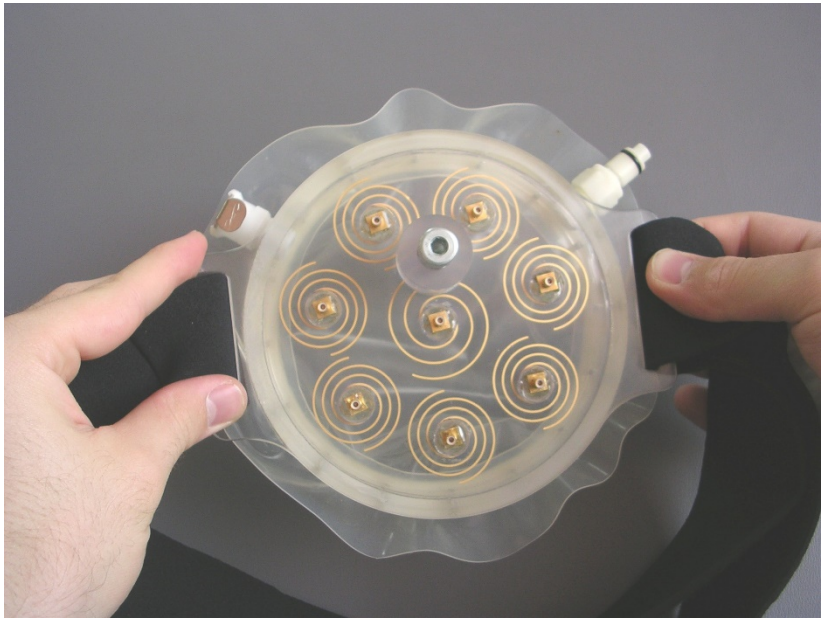
Current microwave systems

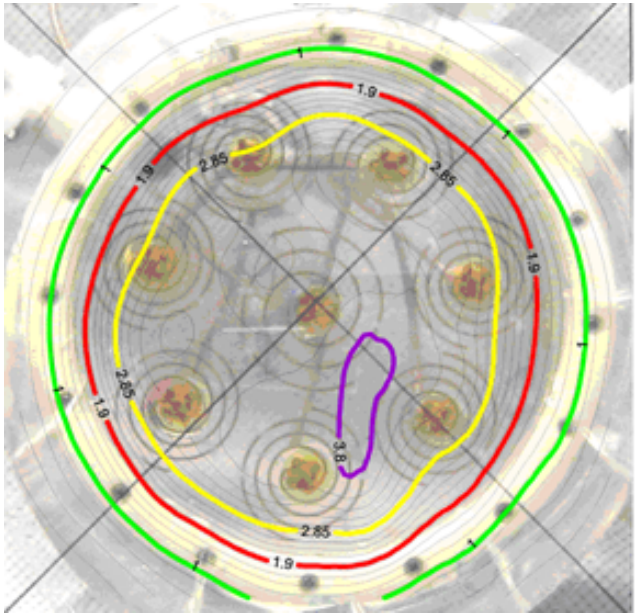
ALBA 434MHz, 0-200Watt, Single Channel, Metal Thermocouples with MW artifact and interference.
Superficial and intracavity, CE Mark

Microwave Future Thoughts

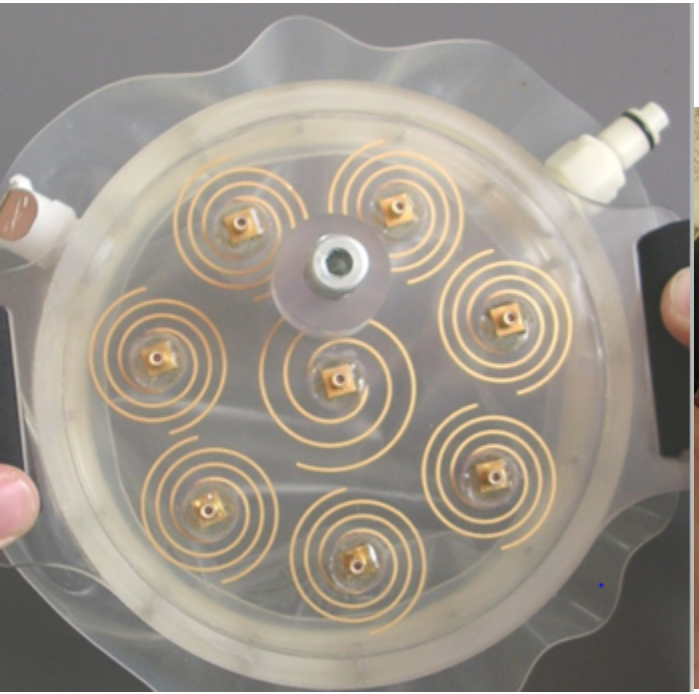
- Superficial arrays for dynamic control of surface temperature distribution
- Improved water bolus interface options
- Pretreatment planning software tools
- More conformal patient interface
- Greater implementation with Brachytherapy

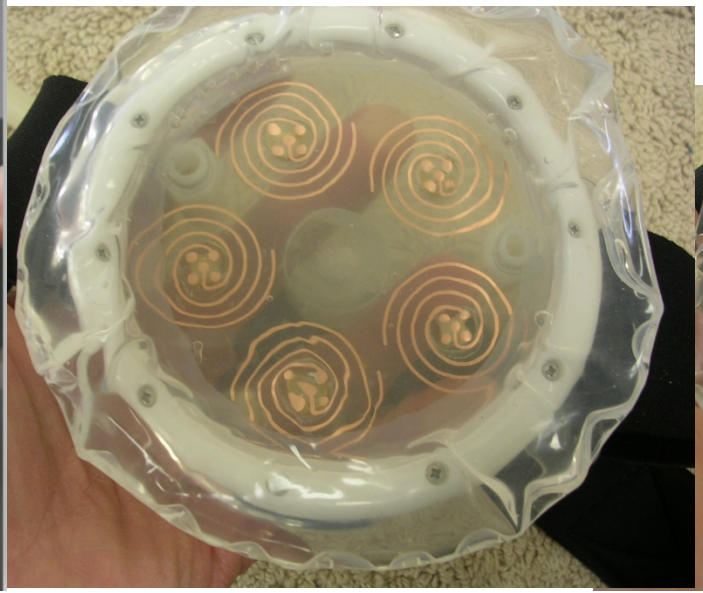
Greater Clinical Use of Microwave Arrays – 8 Spiral Array Being Updated

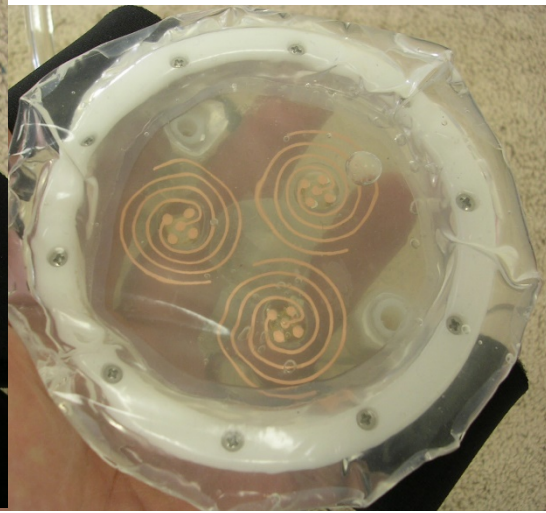




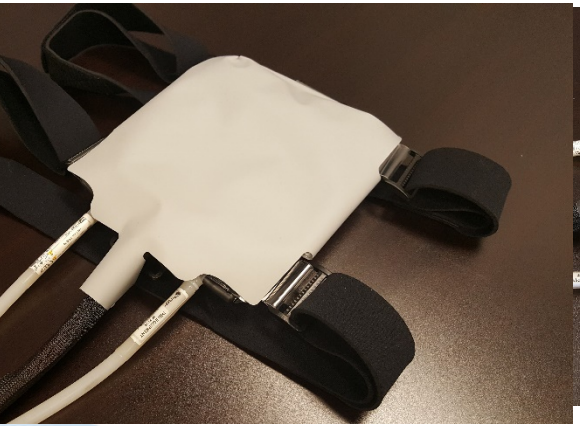
Spiral Arrays of 8, 5 and 3 Spirals For Improved Temperature Uniformity

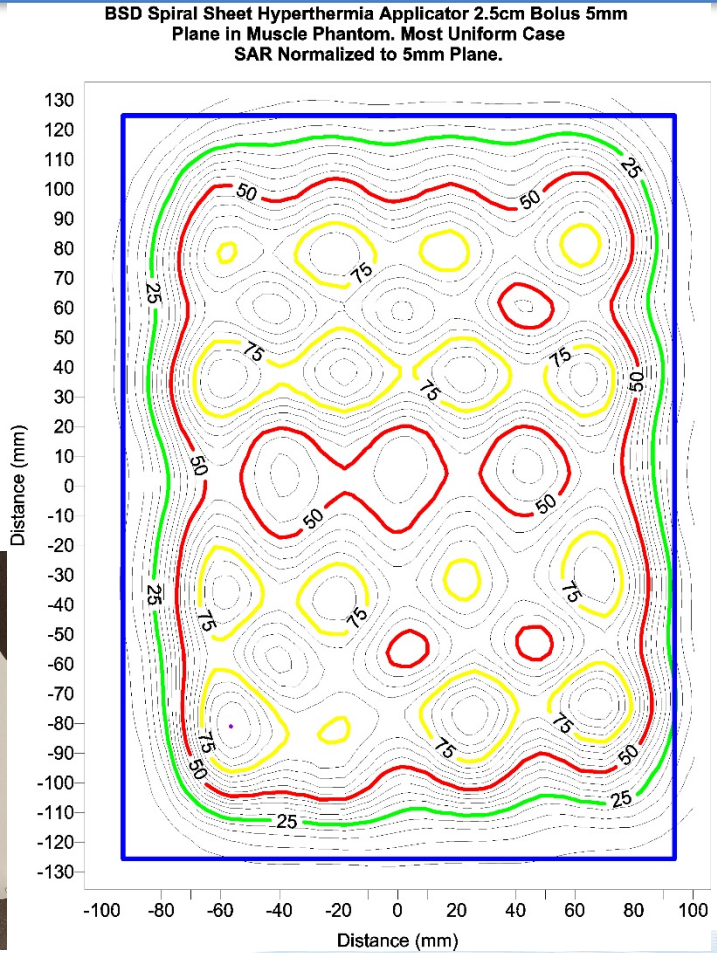






24 Conformal Spiral Array

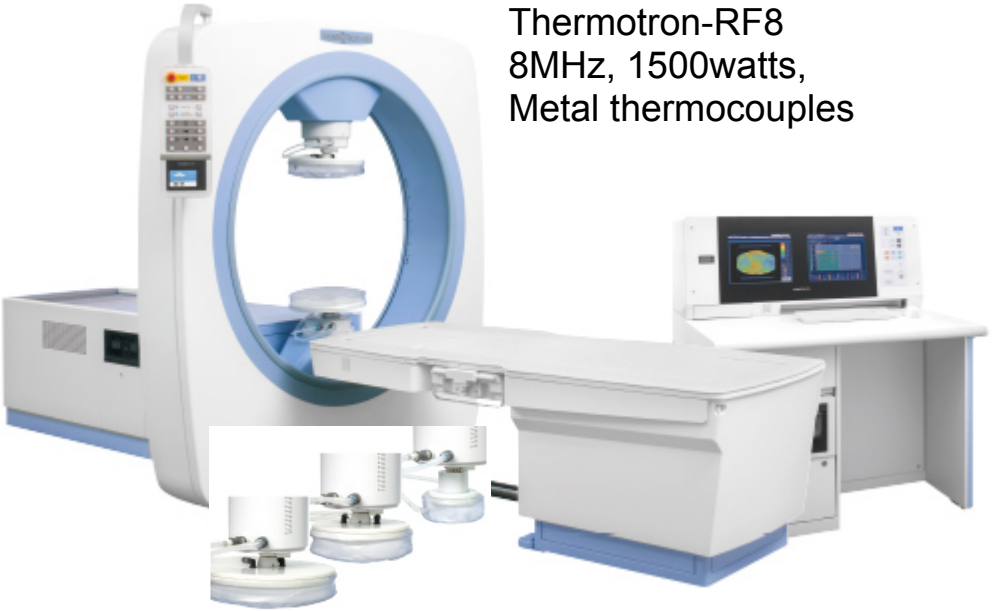




Deep Heating Methods

- RF Capacitive
- RF Phased Array
- HIFU

Oncotherm EHY-2030, 13.56MHz, Protocol 150W Max Power, Generator 600W



Thermotron-RF8
8MHz, 1500watts,
Metal thermocouples

Capacitive electrodes have remained basically the same since 1917 in tumor treatments. Similar to modern toasters evolution.

Some Capacitive Electrodes uses cooling water bolus to reduce excess fat heating with cooling depth limited to 1.5cm of fat.

RF Phased Array Methods

- Surround a body portion with an array of RF field antennas
- Use phase and power control to steering deep focal heating location
- E-field is dominantly parallel to the body to reduce fat heating and boost central focus

Sigma30 (MAPA), SigmaEye, Sigma60

BSD-2000

AMC-4 system 1987
70MHz 4 RF Channels

AMC-8 system
70MHz 8 RF Channels 2 Rings

ALBA 4D, 70MHz, 4Channels 500w each, Metal thermocouples

Awaiting independent clinical validation of this configuration.

Reliability and clinical utility are yet to be established

1981 four waveguide technology has a new look

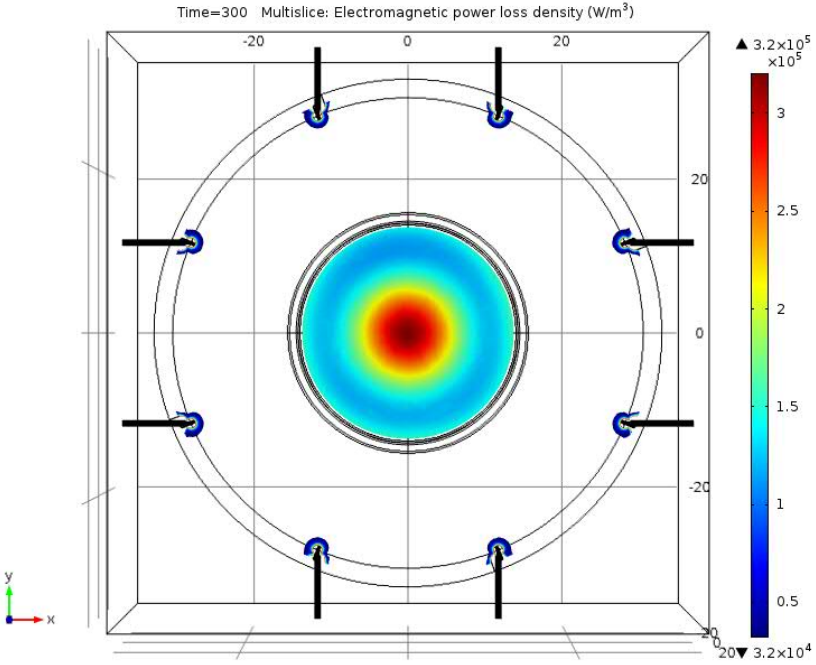
Deep Heating Numerical Study

- COMSOL 3D Multiphysics Model
- Homogeneous phantom cylindrical and elliptical saline or muscle dielectric and 2/3rds muscle conductivity with 1cm layer of superficial fat.

Sigma 60-8 dipole array@ **100MHz** using a COMSOL numerical model of a 28cm diameter phantom 74cm long & 48cm long water bolus.

This study showed more selective central heating
with low fat heating near the bolus outer edges.
Maximum SAR is shown in the tissue center.

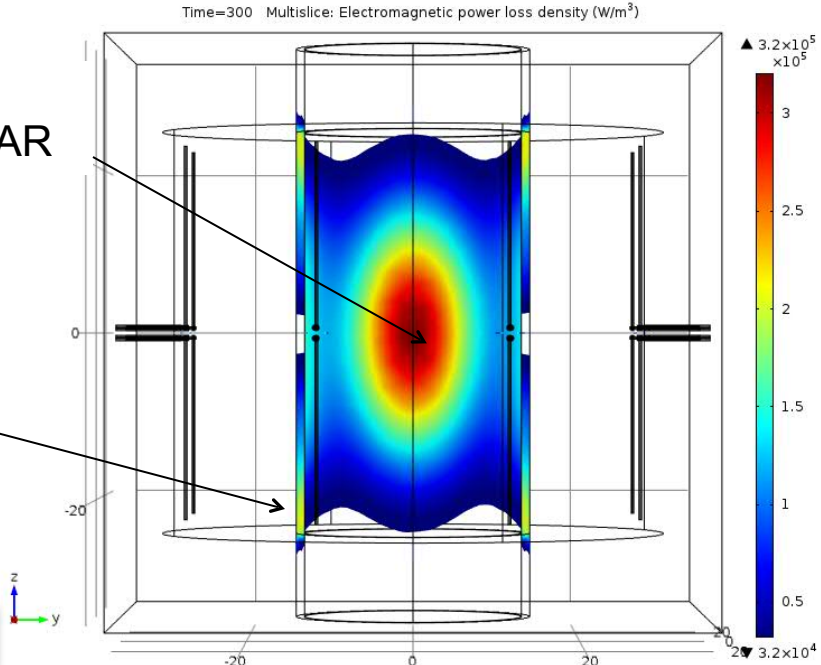
Axial Slice View



Coronal Slice View

100%
Central SAR

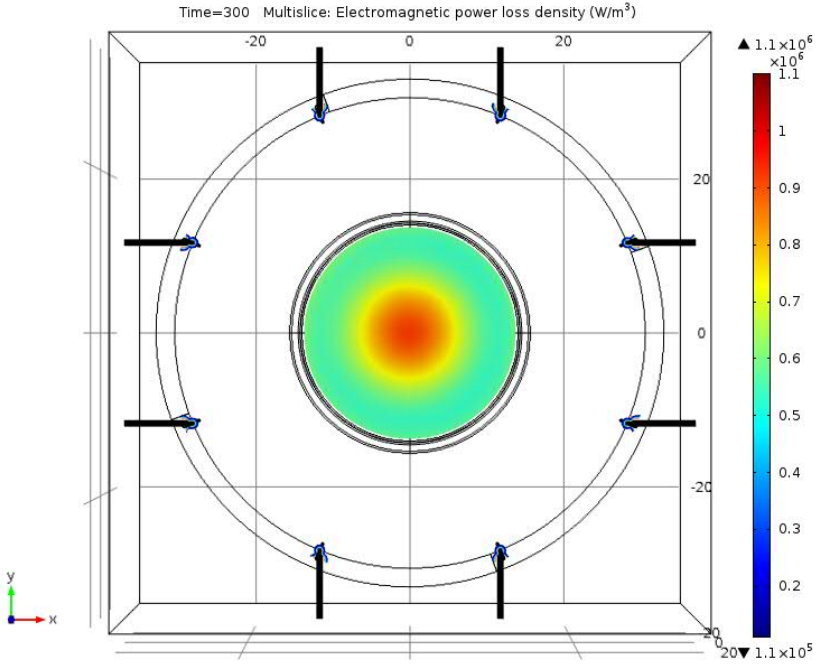
50%
Fat SAR



Sigma 60-8 dipole array@ **75MHz** using a COMSOL numerical model of a 28cm diameter phantom 74cm long & 48cm long water bolus.

This study showed stable and uniform surface and central heating with and increase of fat heating near bolus outer edges as compared with the heating at the center.

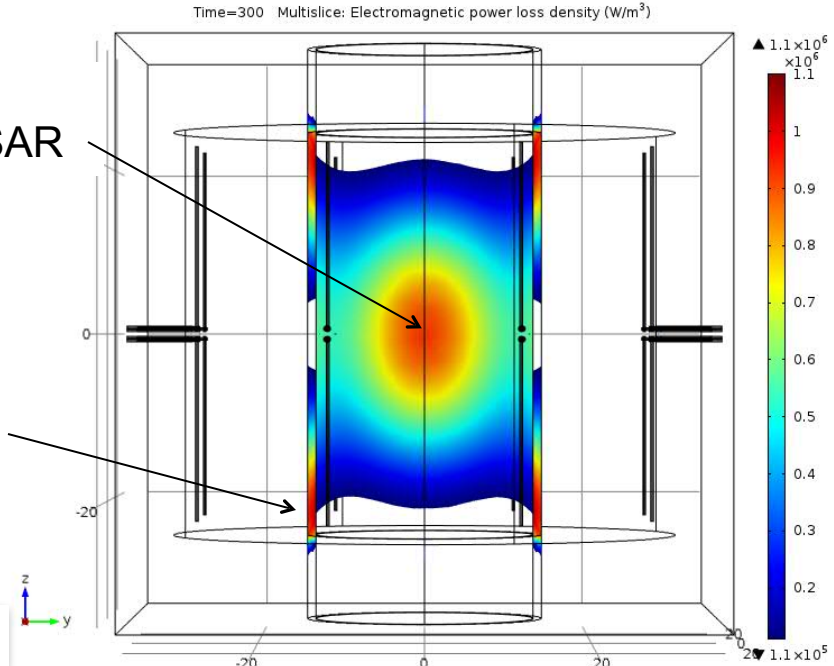
Axial Slice View



Coronal Slice View

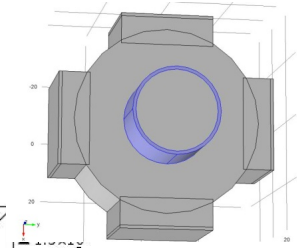
85% Central SAR

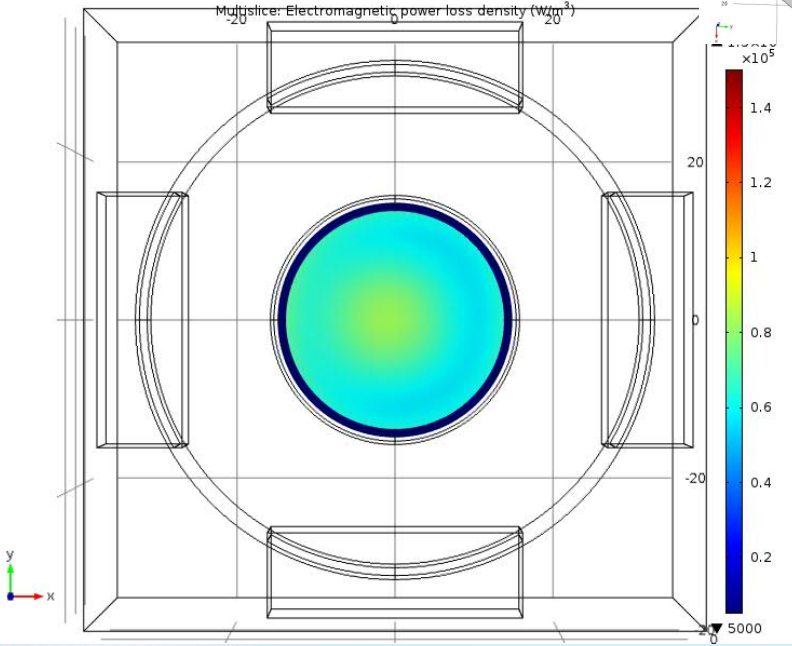
100% Fat SAR



AMC-4 Waveguide array@ **70MHz** using a COMSOL numerical model of a 28cm diameter phantom 74cm long & **40cm** long water bolus. This study showed high superficial fat SAR potential.

Axial Slice View

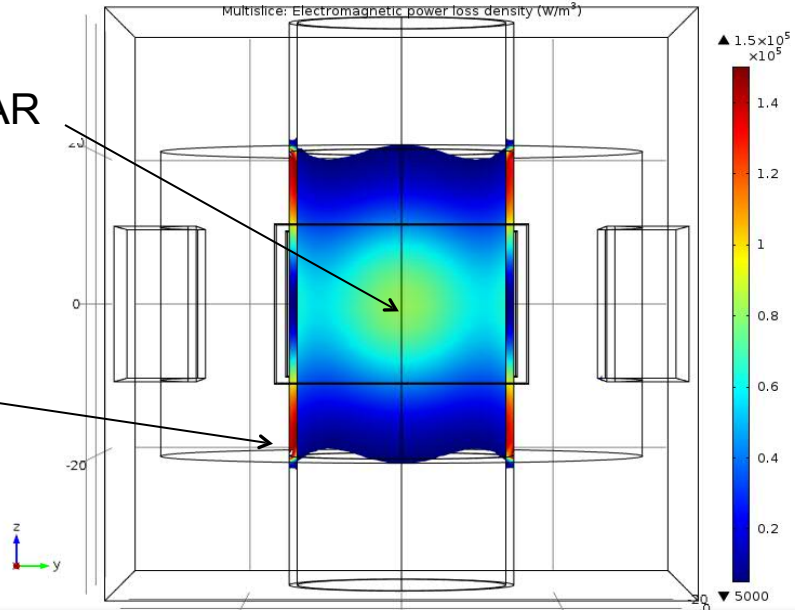




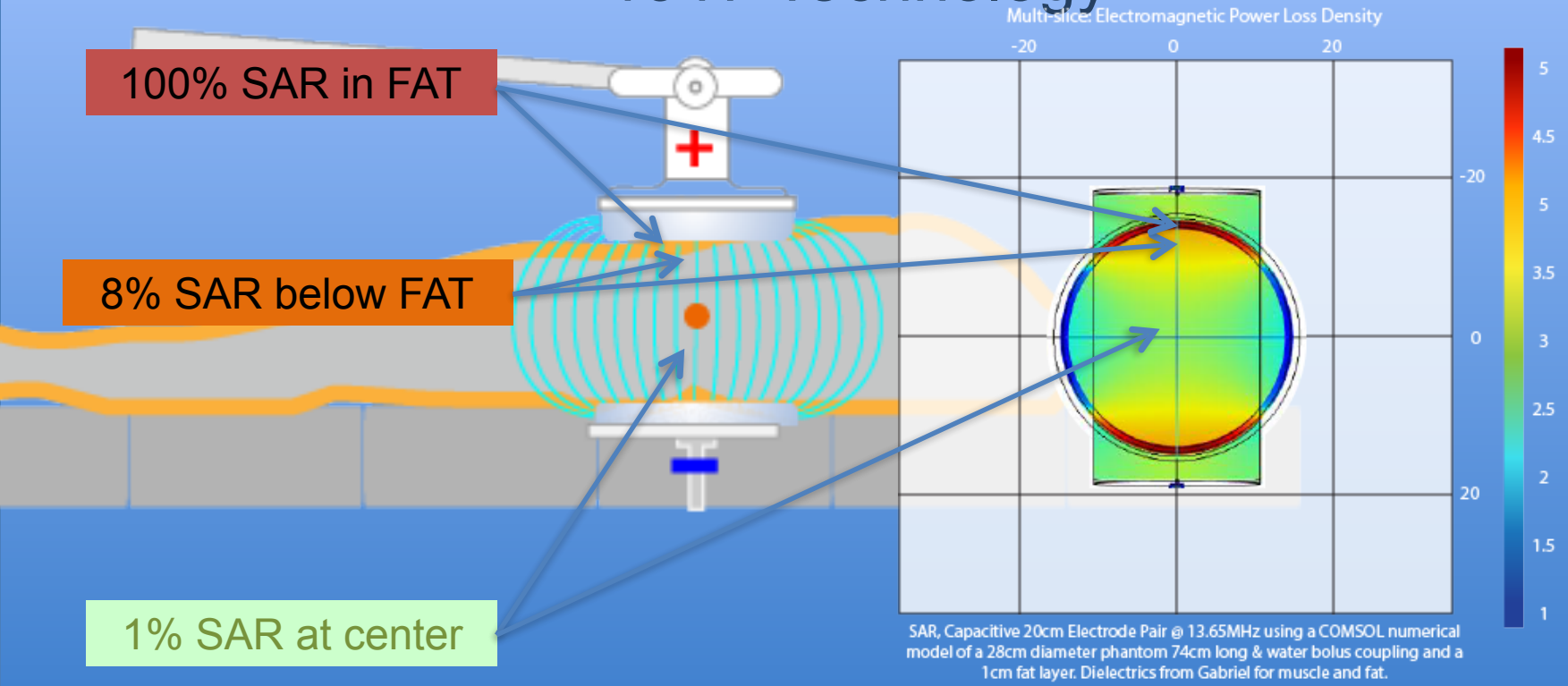
50%
Central SAR

100%
Fat SAR

Coronal Slice View



Capacitive Electrodes Have No Energy Focus
1917 Technology

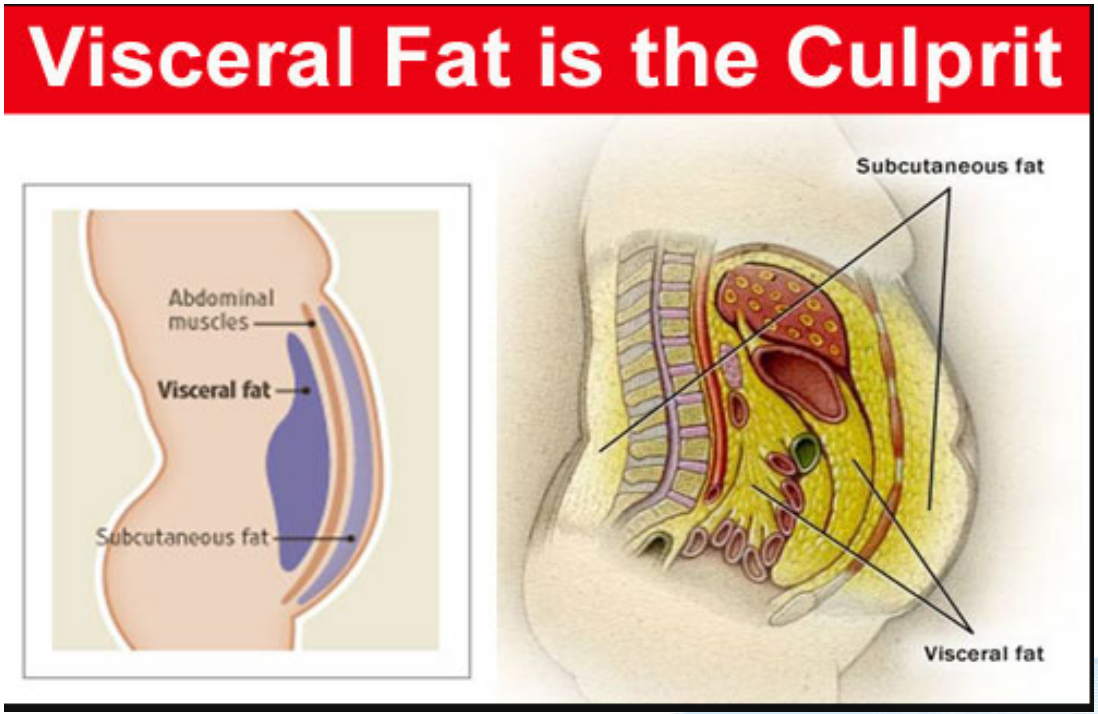


SAR, Capacitive 20cm Electrode Pair @ 13.65MHz using a COMSOL numerical model of a 28cm diameter phantom 74cm long & water bolus coupling and a 1cm fat layer. Dielectrics from Gabriel for muscle and fat.

Capacitive field divergent current

- If RF currents diverge 1.7 times the electrode diameter at depth, the expanding area at depth is $(1.7)^2 = 2.9$ times larger at the phantom center, so the RF current is 1/2.9 times less than under fat.
- SAR= I^2R= $(1/2.9)^2$ R= R/8= $1/8^{th}$ of the muscle surface.
- For heating a central tumor or for a possible non-thermal modulation effect, the RF power must reach the target with an adequate level to be effective.

RF currents from capacitive electrodes will only converge if bone, fat, and air regions divert these currents to concentrate them. The visceral fat distribution is unique to a patient and limits any consistent deep heating results from capacitive electrodes in patients with visceral fat.



There is a limited future for capacitive electrodes in deep heating

- Superficial fat layer absorption
- Field shape is divergent with lack of control
- RF current flow paths are altered by visceral fat
- Not compatible with image guided SAR steering
- Dump and pray for an RF conductive path to reach the tumor

The Future is Phased Arrays For Deep Heating

SigmaEllipse

BSD-2000

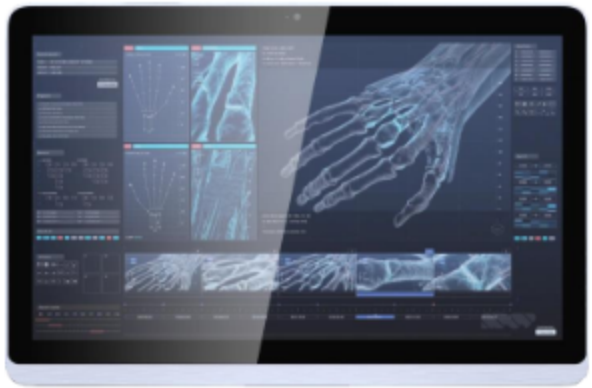
BSD-2000 3D/MR System

- 1997 - Munich - Siemens 0.2T
- 2001 - Berlin - Siemens Symphony 1.5T
- 2007 - Erlangen - Siemens Symphony 1.5T
- 2008 - Dusseldorf - Siemens Symphony 1.5T
- 2009 – Duke University - GE Signa HDxt 1.5T
- 2011 - Tübingen - Siemens Symphony 1.5T
- 2014 - Rotterdam – GE 450W 1.5T
- 2017 – Munich – Philips Ingenia 1.5T

2017 Munich Installation

- Universal System approved for clinical use

2019 New Developments In Process

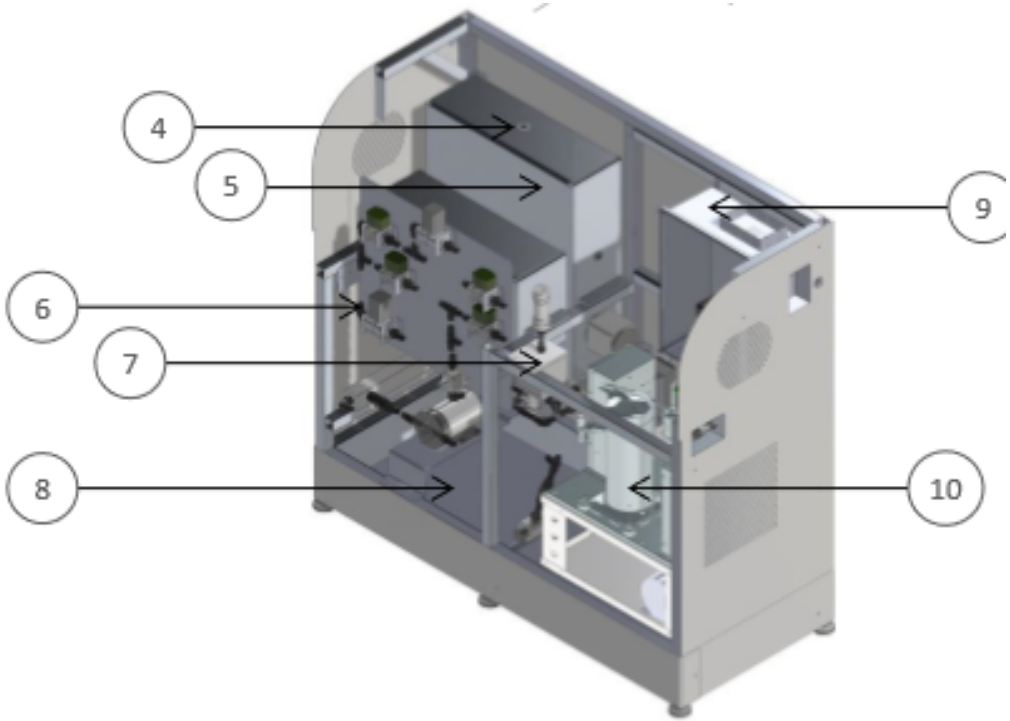


-Universal Water System Design
-Software Controls for Universal Water System
-All-In-One Computer/Desktop Console

New BSD-2000 MR Water System

Major Improvements

- Improved Air Removal and Pressure Monitoring *(7)*
- Leak Catch Tub and Leak Detection *(8)*
- On-Board 1 Ton Chilling Unit for Improved Site Flexibility *(10)*
- Sensor Additions allow for Software Functionality Improvements without updated Hardware:
  - Possibility for automated Fill/Drain Capability
  - Possibility for automated Bolus Air Removal
- Addition of Pedestal LED Flow Indicator
- Addition of System Control Function Buttons on Electrical Box for Quick Troubleshooting
- No Need for Deionizing Filter due to Closed System Architecture – Breathable .3µm Filter Resists Contamination *(4)*
- 3 Separate Water Level Sensors for Improved Communication to Operator and Smart Controls *(5)*
- Added Ability to Drain and Refill System from Pedestal
- Adjustable Chilled Water Source Temperature for Patient Comfort during Circulation



BSD-2000 Hyperthermia System TEST

Hyperthermia Treatment

Planning

Sensor Setup

Recall

Utilities

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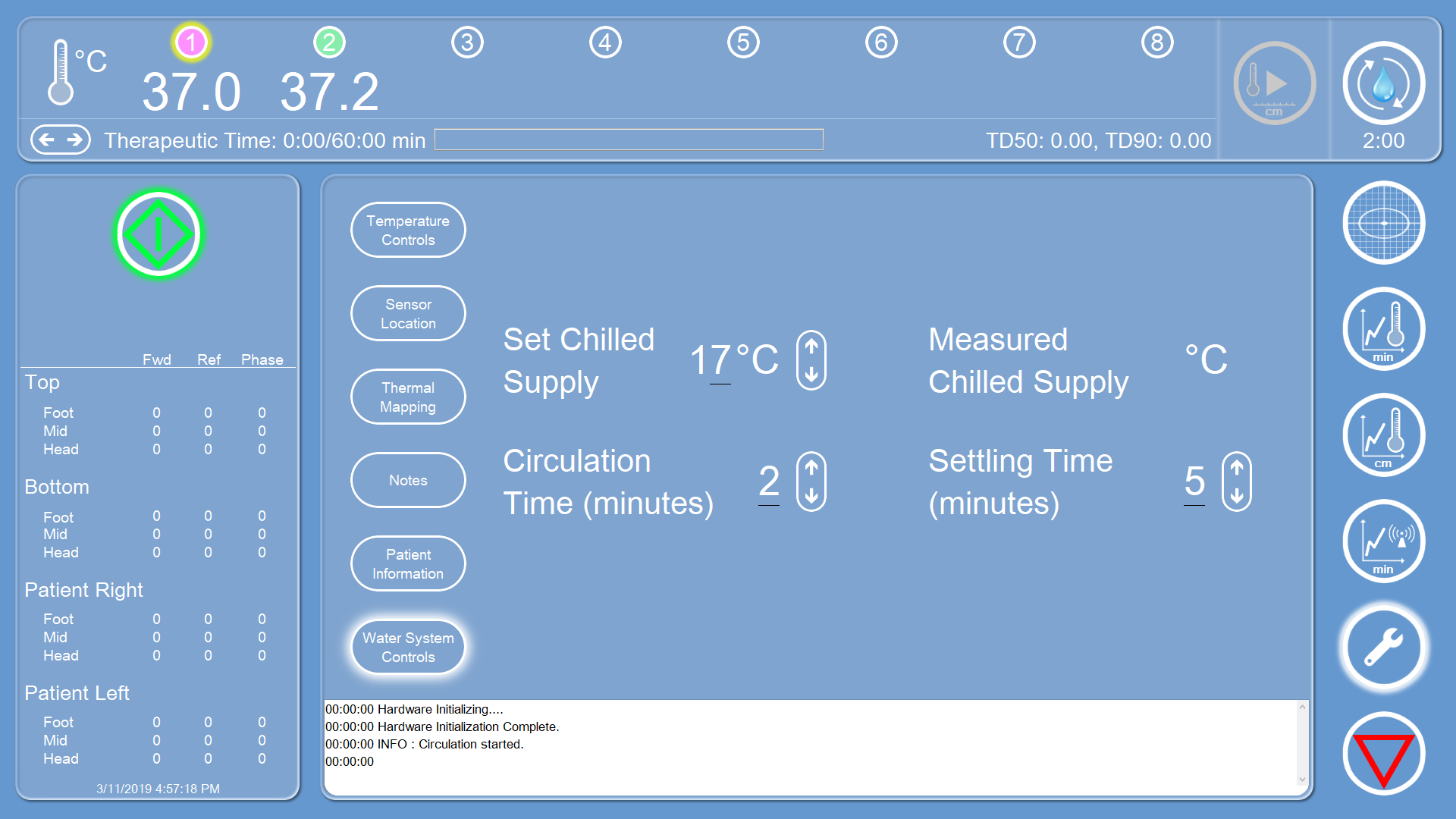
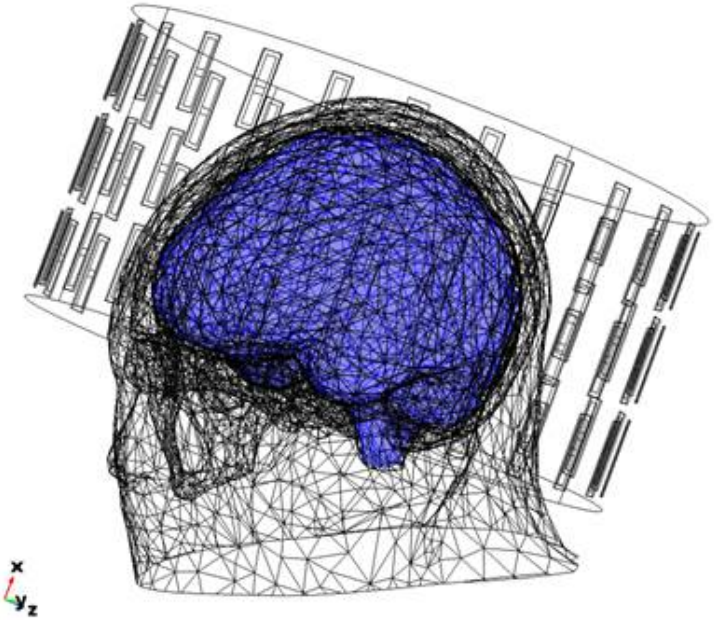
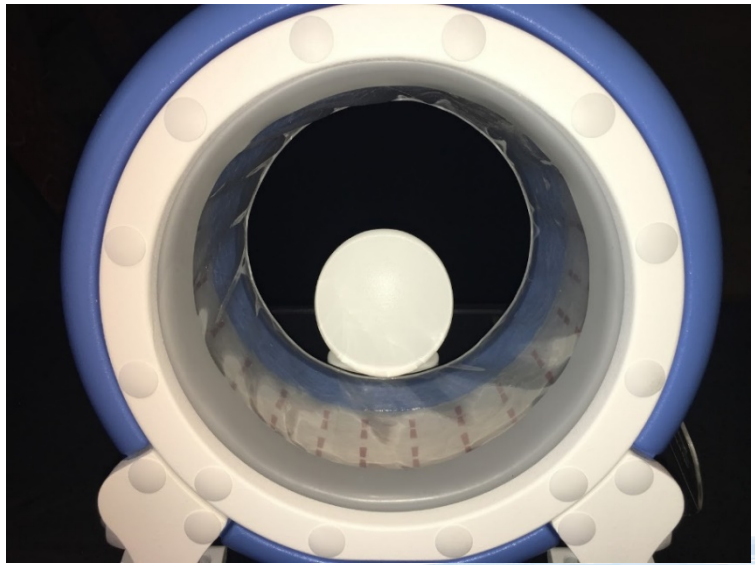
Shutdown


°C
1
2
3
4
5
6
7
8
37.0
37.2
Therapeutic Time: 0:00/60:00 min
TD50: 0.00, TD90: 0.00
cm
2:00
Fwd Ref Phase
Top
Foot 0 0 0
Mid 0 0 0
Head 0 0 0
Bottom
Foot 0 0 0
Mid 0 0 0
Head 0 0 0
Patient Right
Foot 0 0 0
Mid 0 0 0
Head 0 0 0
Patient Left
Foot 0 0 0
Mid 0 0 0
Head 0 0 0
3/11/2019 4:57:18 PM
Temperature Controls
Sensor Location
Thermal Mapping
Notes
Patient Information
Water System Controls
Set Chilled Supply
17 °C
Measured Chilled Supply
°C
Circulation Time (minutes)
2
Settling Time (minutes)
5
00:00:00 Hardware Initializing....
00:00:00 Hardware Initialization Complete.
00:00:00 INFO : Circulation started.
00:00:00
min
cm
min

Noninvasive brain applicator Hal.o

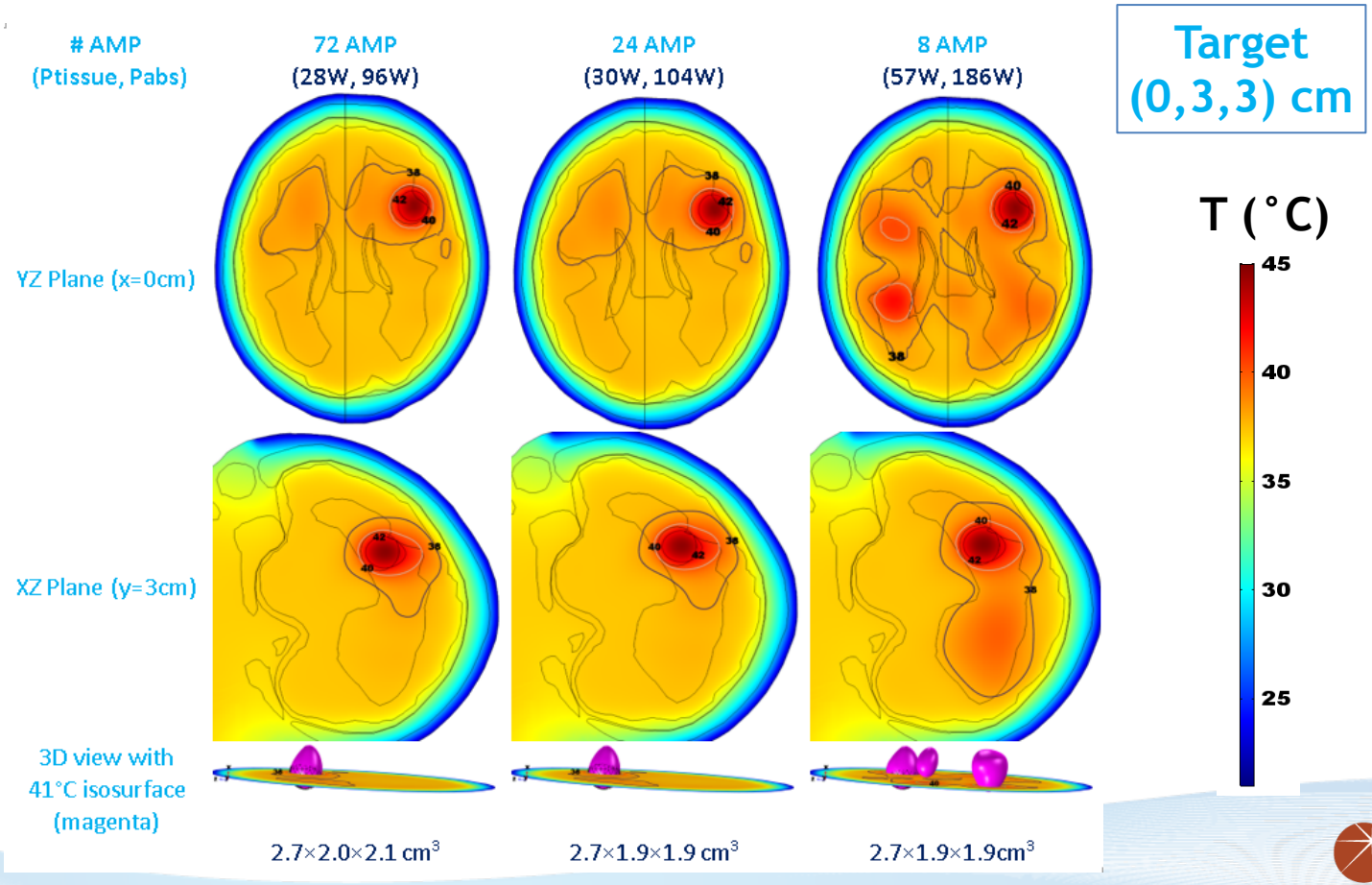
- Operating frequency: 915 MHz
- Array: 3 rings of 24 antennas (dipole size 9×24 mm)
- Cylindrical frame: 13 cm length, 26 cm dia. (~4cm water bolus)





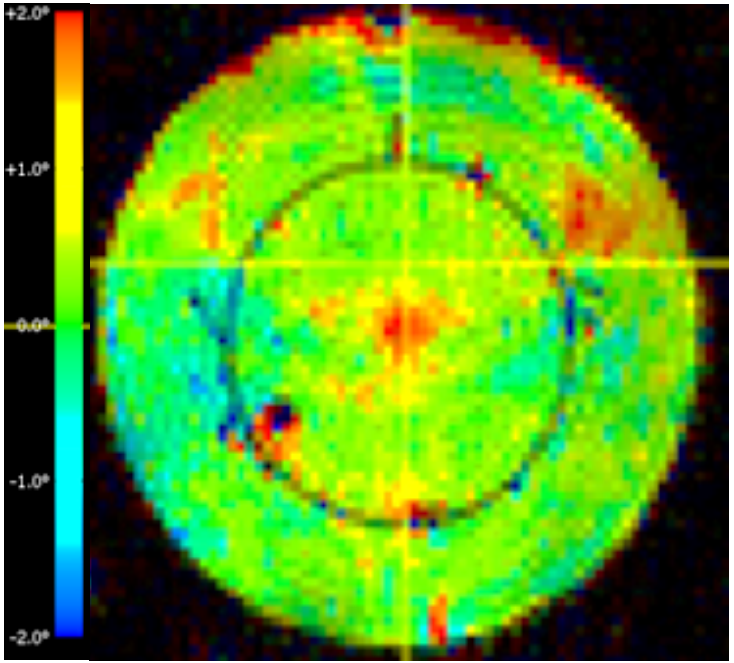
Patent pending

Steering with different number of amplifiers



Sim vs **Exp** MR thermometry after 3min of heating target (0,0,0)

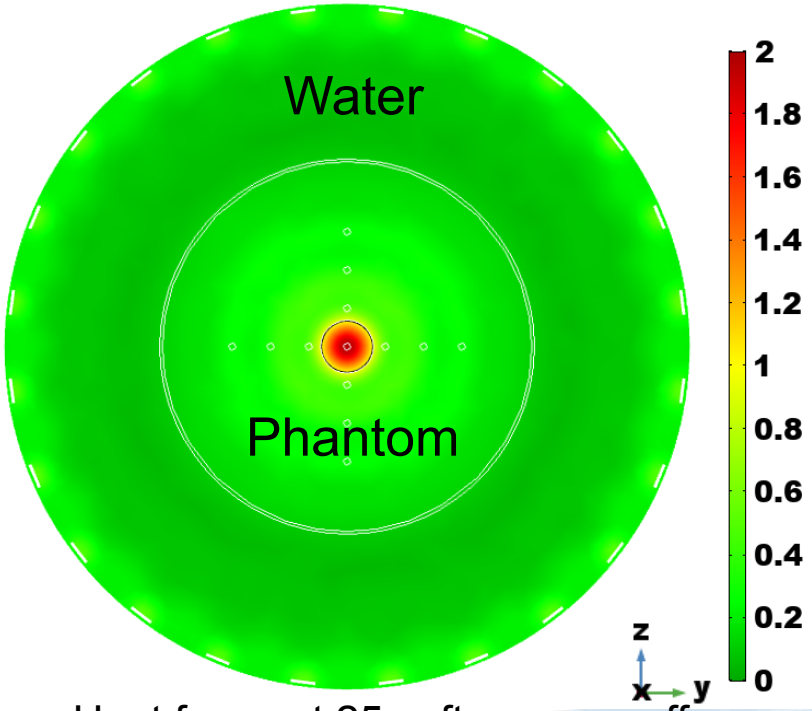
MR thermometry



Heat focus ~25s after power off

4 × 2 × 2 cm³

Simulation



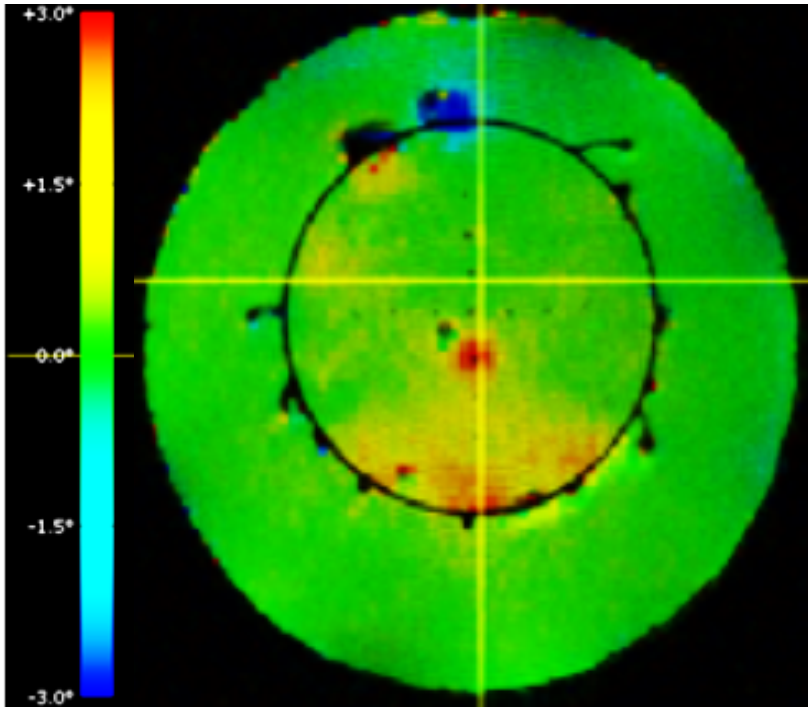
Heat focus at 25s after power off

3.9×1.9×1.9 cm³

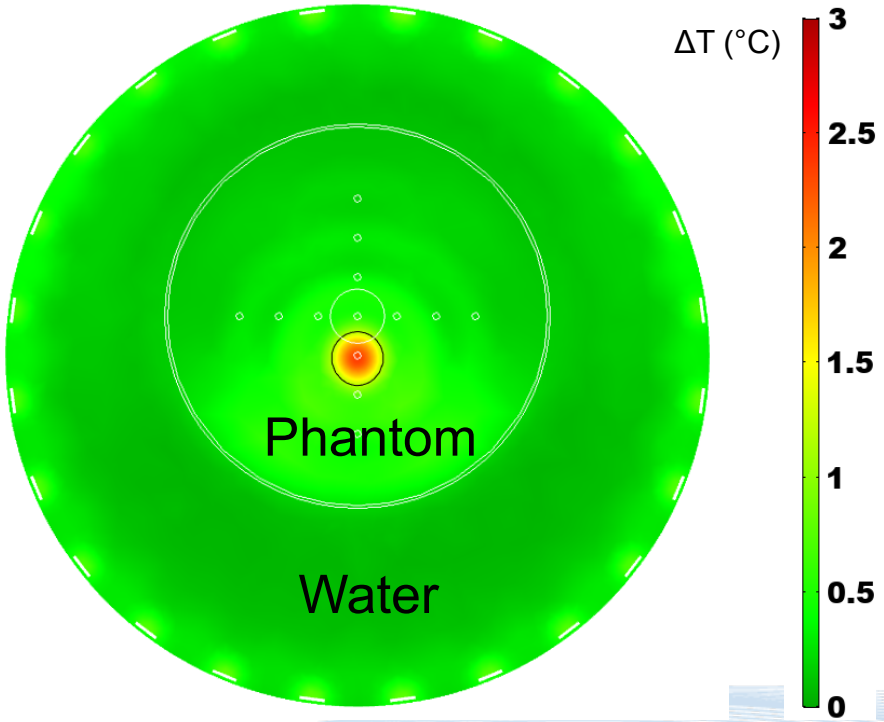
Sim vs **Exp** MR thermometry: Mechanical steering

Phantom shifted vertically 1.5 cm → Focus is kept at the applicator center

MR thermometry



Simulation



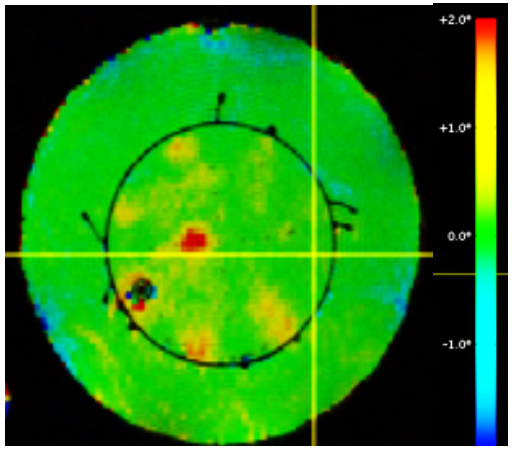
$\Delta z_{focus,exp}$ = 1.5 cm

Making A Difference in Cancer Care

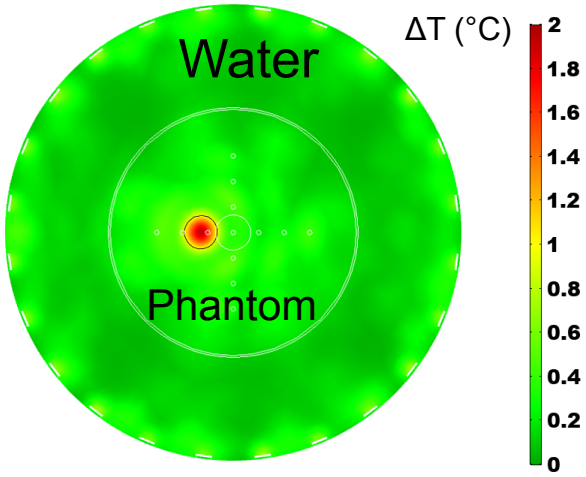
$\Delta z_{focus,sim}$ = 1.5 cm

Pyrexar MEDICAL

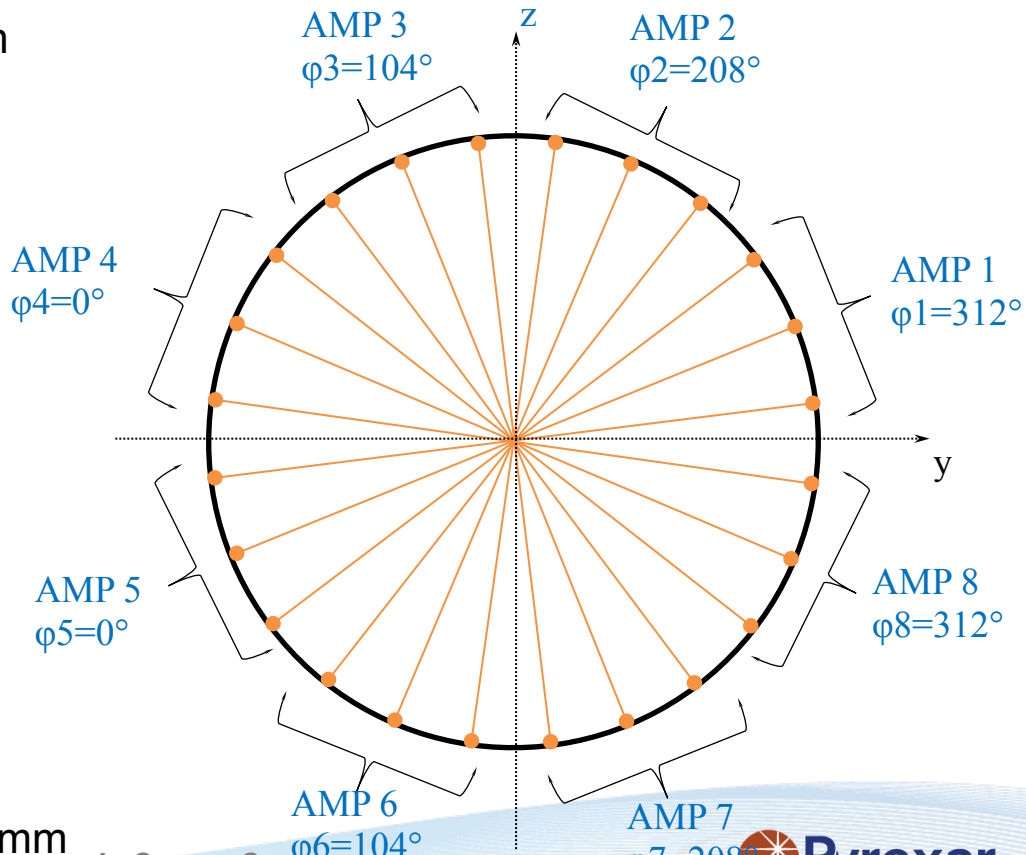
Sim vs **Exp** MR thermometry: Electronic phase steering



Δy(exp) = 16 mm

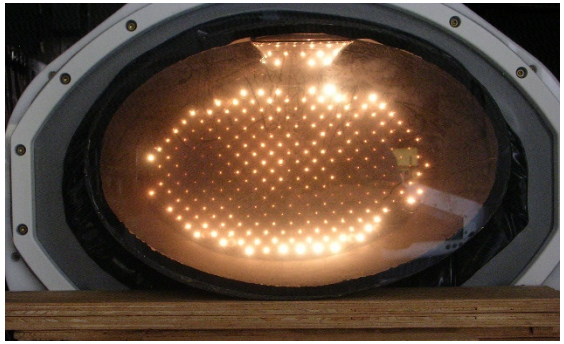


Δy(sim) = 18 mm

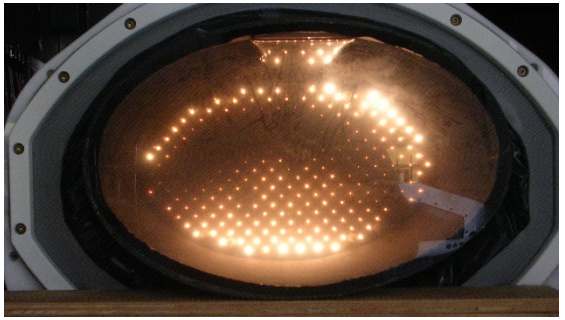


New deep heating practices

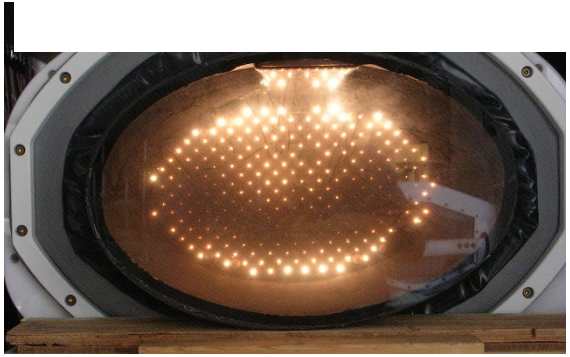
- Non-centered patient phase steering
- Superficial heating by power control
- Future MR image guided treatment optimization.



Vertical phantom +2cm
(0,5) cm focus
(0,5)-(0,2)=(0,3)

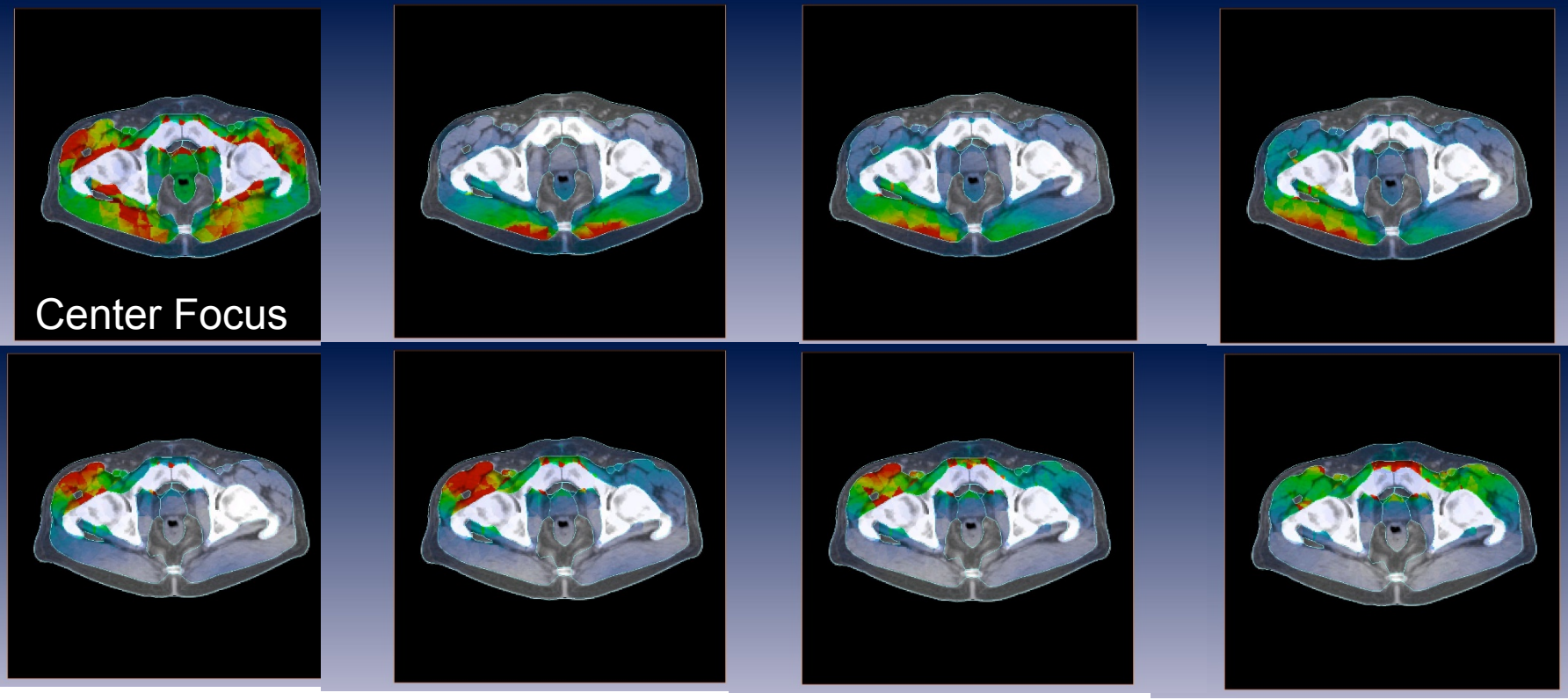


Vertical phantom +2cm
(0,-1) cm focus
(0,-1)-(0,2)=(0,-3)



Centered phantom
(0,3) cm focus

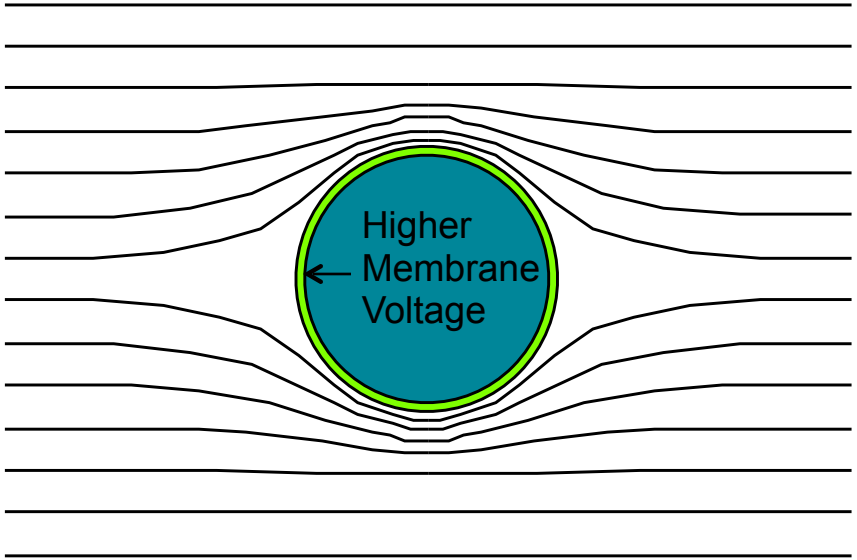
Centered phantom
(0,-3) cm focus



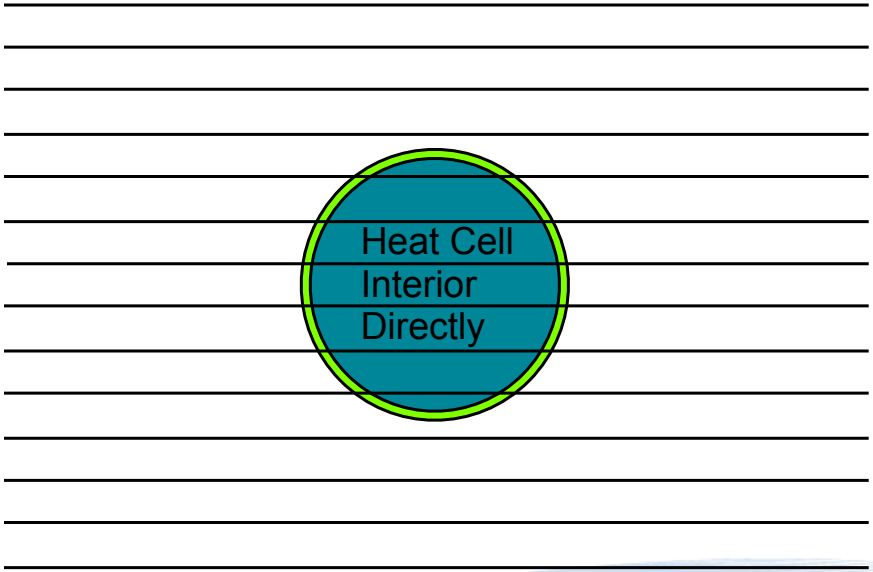
Sigma 60 Superficial SAR Prediction at 90MHz by SigmaHyperPlan
Using RF Power On Only 1 or 2 Power Channels

Future developments need to understand frequency dependence of field interaction caused by the cell membrane

0.1 to 100MHz RF currents flow around the cell

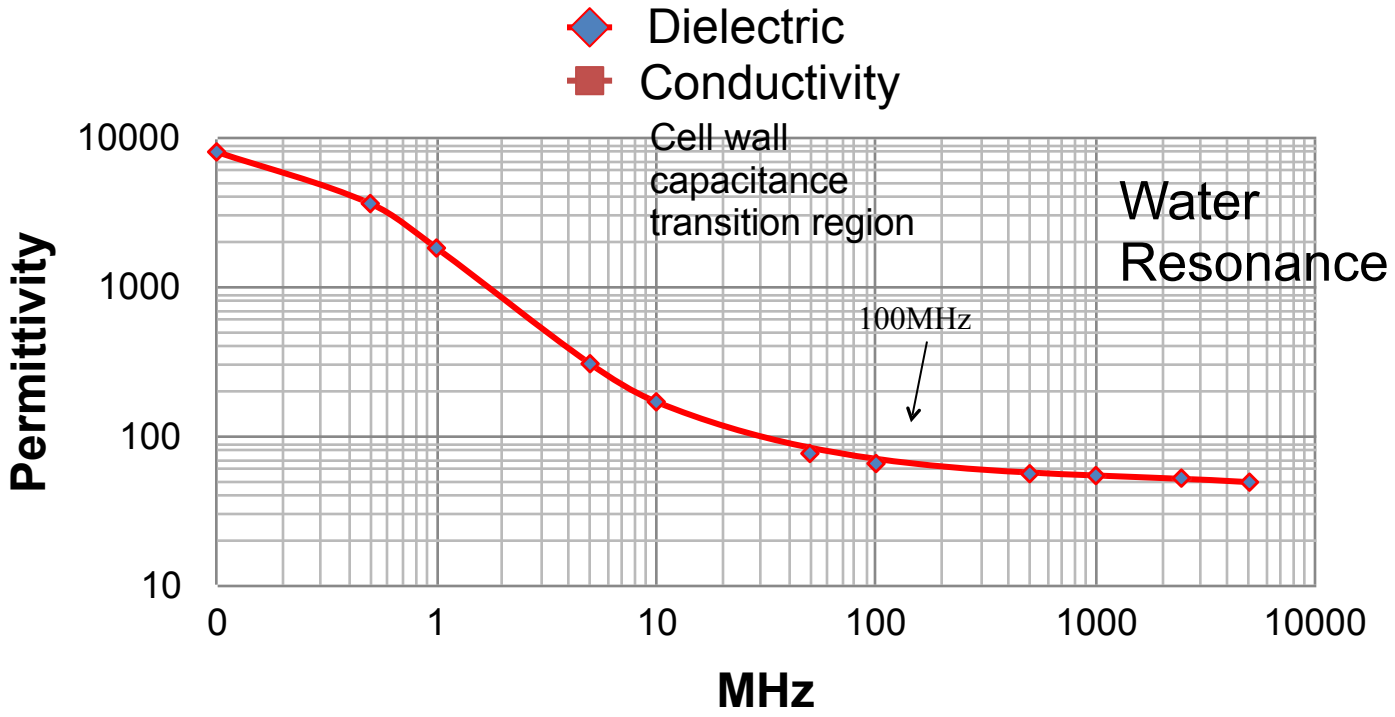


High Microwave Frequency currents pass through the cell >100MHz



R. Pethig, Dielectric and Electronic Properties of Biological Materials, John Wiley & Sons, 1979

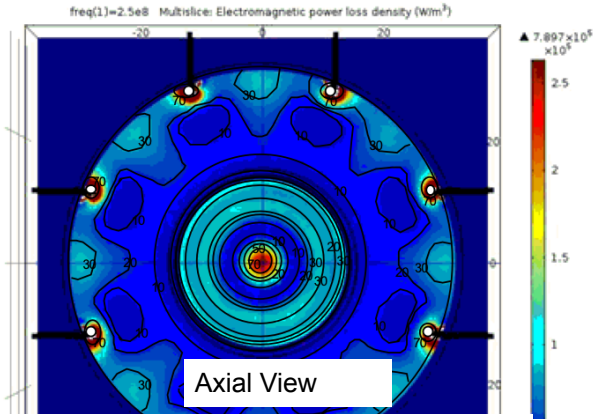
Muscle Tissue Dielectric and Conductivity Due to Cell Membrane Capacitance and Water Resonance



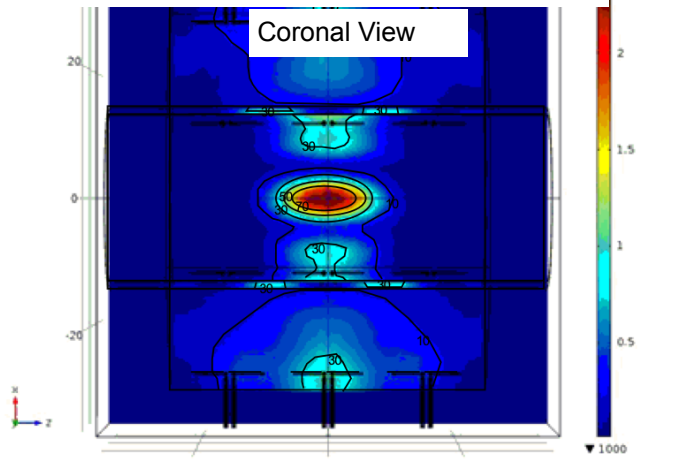
R. Pethig, Dielectric and Electronic Properties of Biological Materials, John Wiley & Sons, 1979

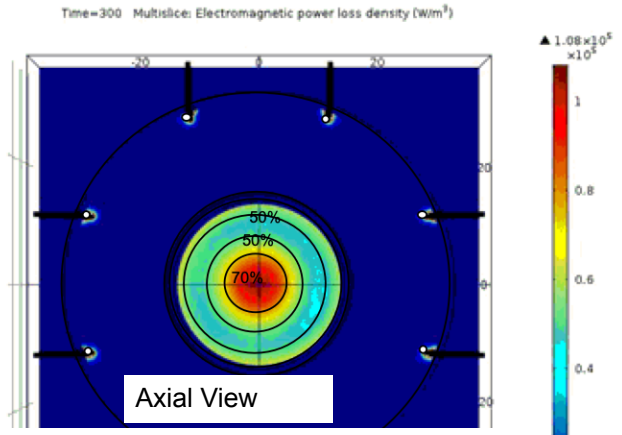
Numerical Advanced Study

- COMSOL 3D Multiphysics Model
- Homogeneous phantom cylindrical and elliptical saline or muscle dielectric and 2/3rds muscle conductivity with 1cm layer of superficial fat.
- More than 300 solutions with different variations evaluated.

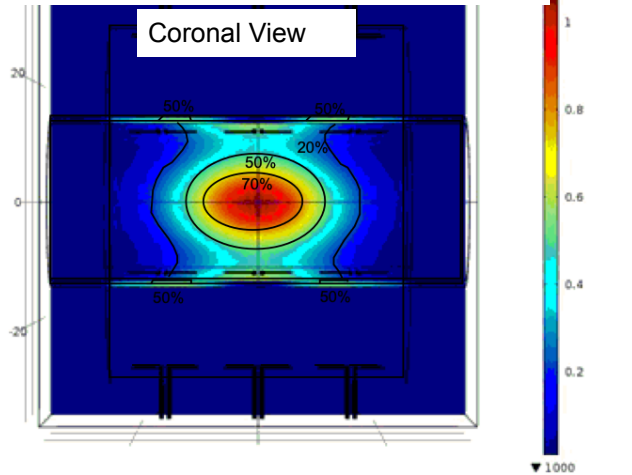


250MHz, Center focus,
24 dipoles & RF channels , PG bolus,
saline phantom, **Vol. 206cc**





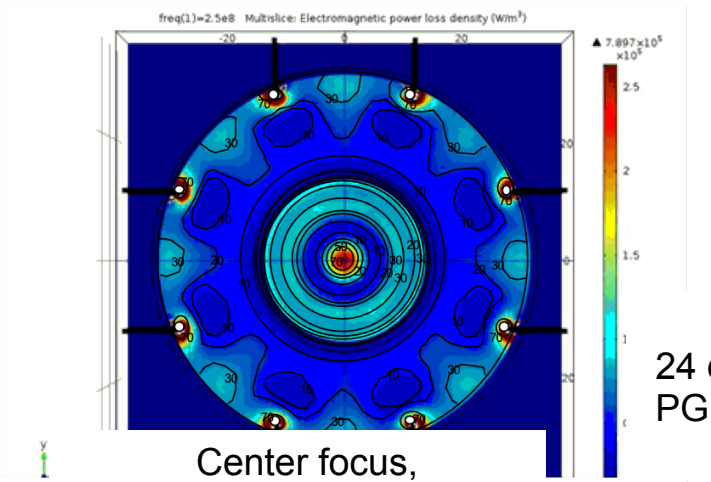
100MHz, Center focus,
24 dipoles & RF channels , Water bolus,
saline phantom, **Vol. 1957cc**



Patent pending

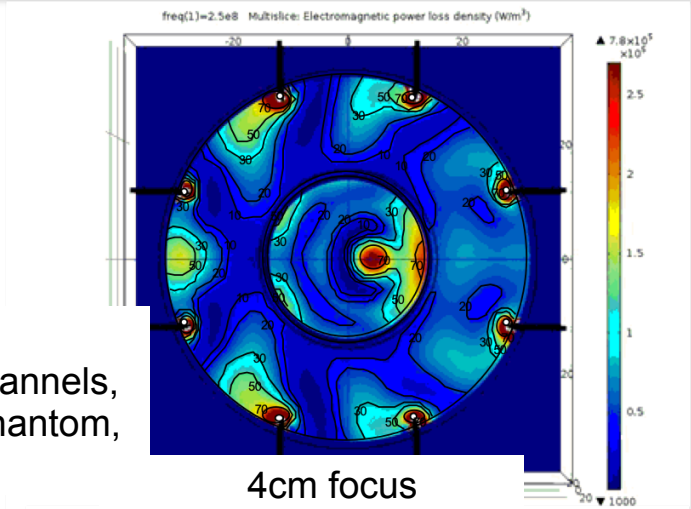
aking A Differenc

Tyrexar MEDICAL

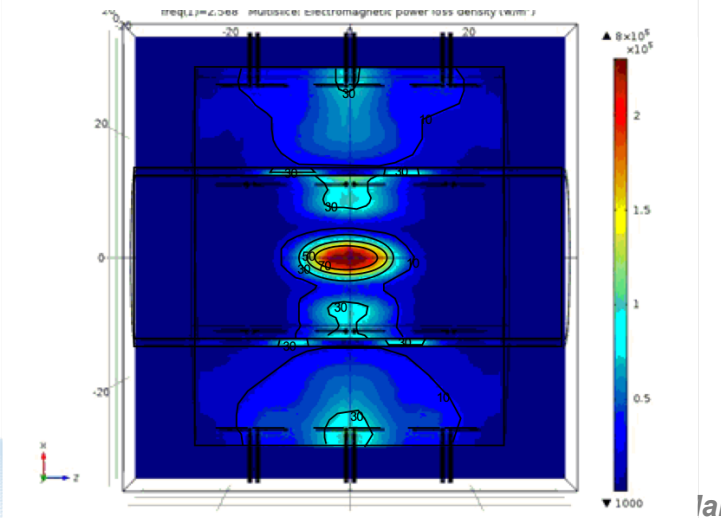


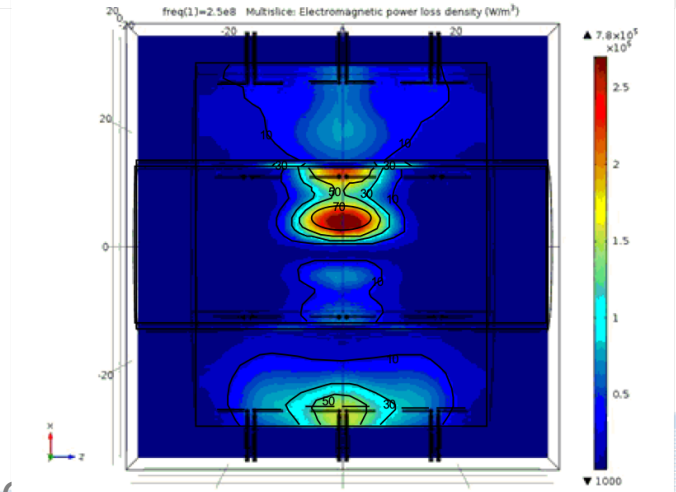
Center focus,

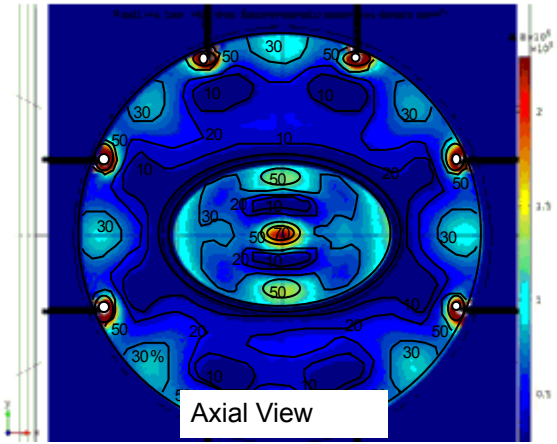
250MHz,
24 dipoles & RF channels,
PG bolus, saline phantom,
Vol. 206cc

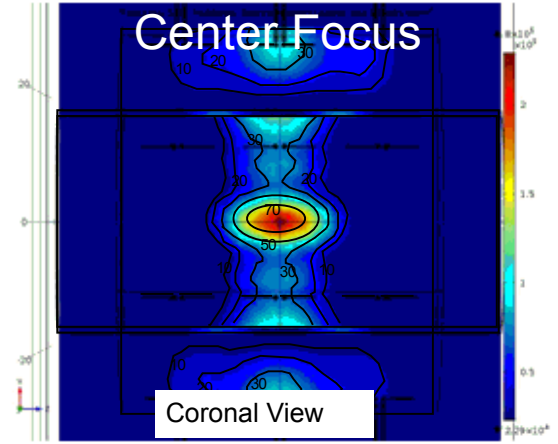


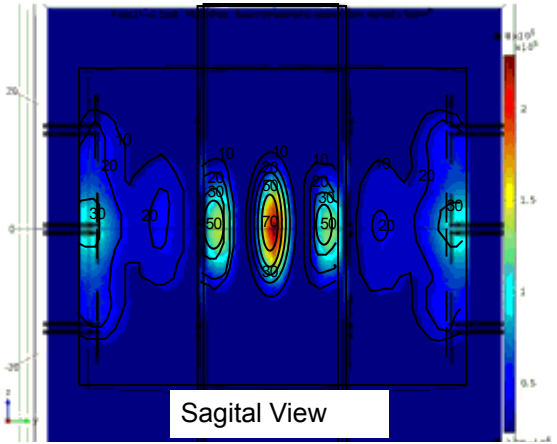
4cm focus



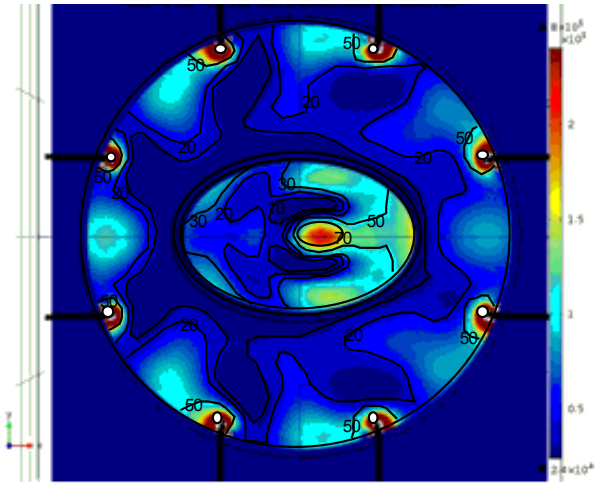


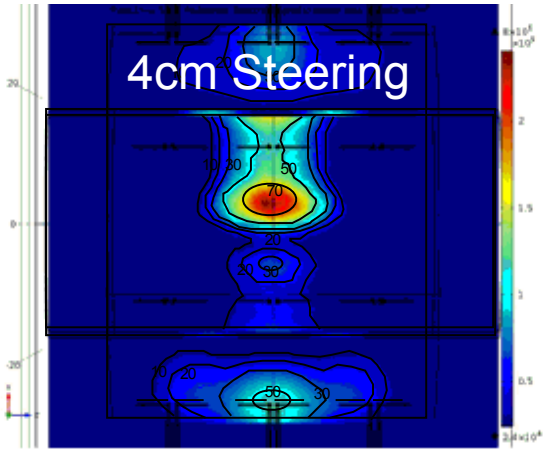


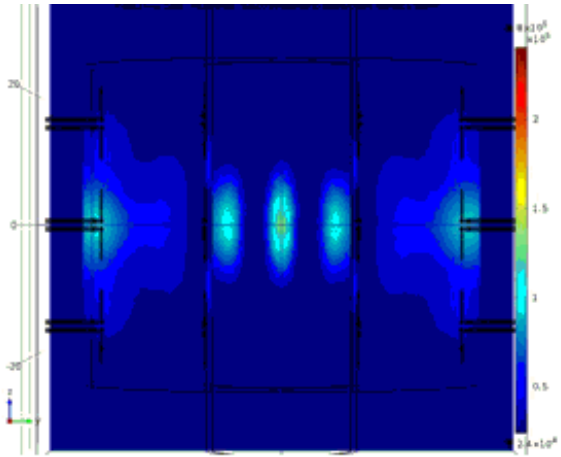


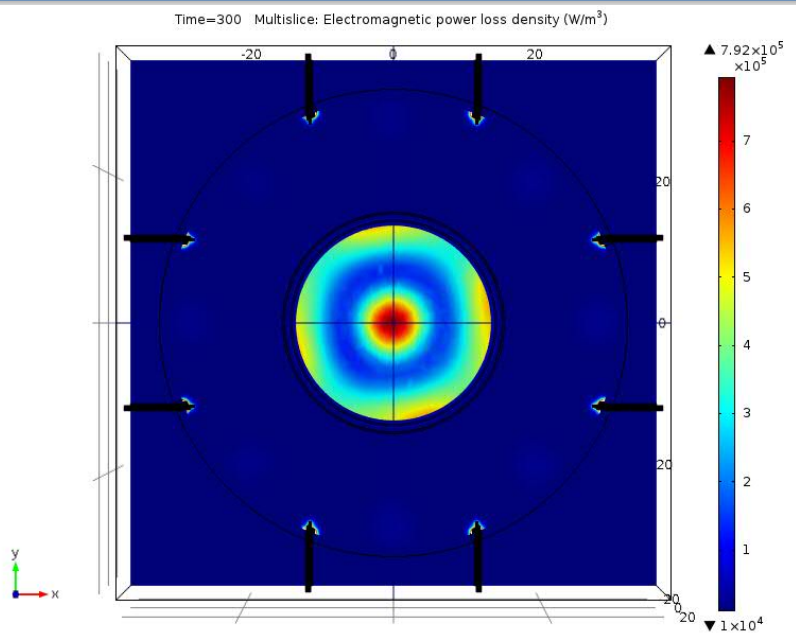


250MHz, **Propylene glycol** bolus 24 dipoles & channels, muscle phantom, **Vol=176cc**

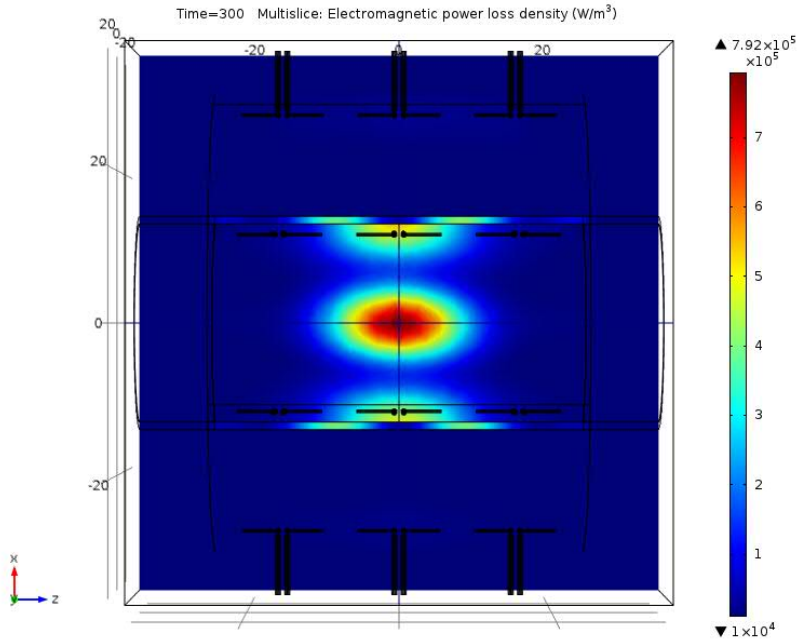






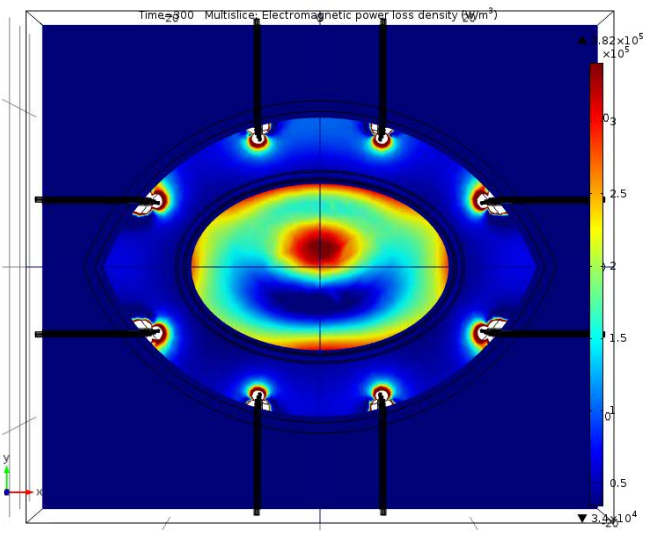


Axial

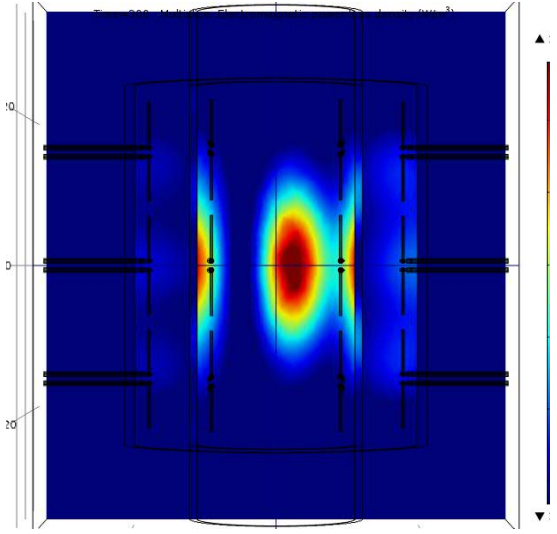


Sagital

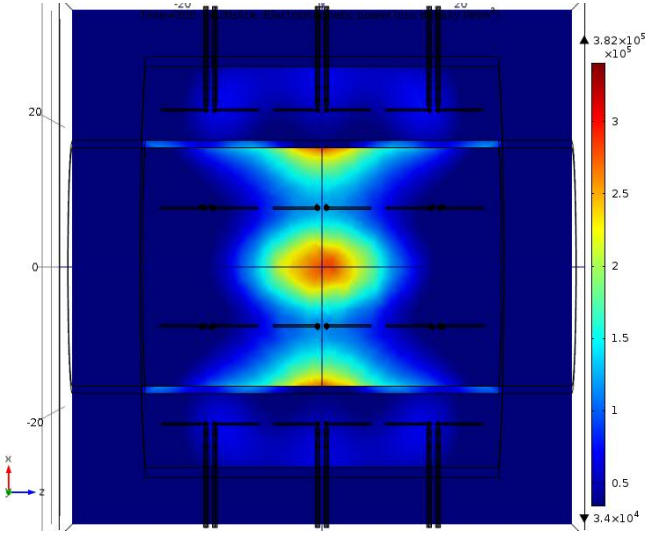
175 MHz Axial View, 3D Optimization Central Focus
24 channels and dipoles, 10.6 cm dipoles,
48 cm wide bolus, 60 cm dia. water bolus.
6.9x6.9x13.4cm, Vol.= 334cc



Axial

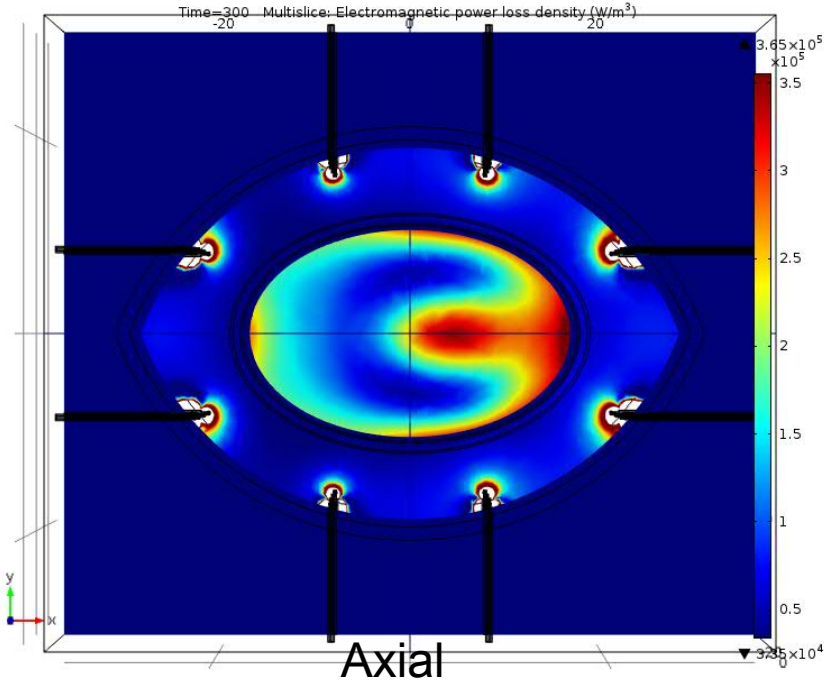


Sagital

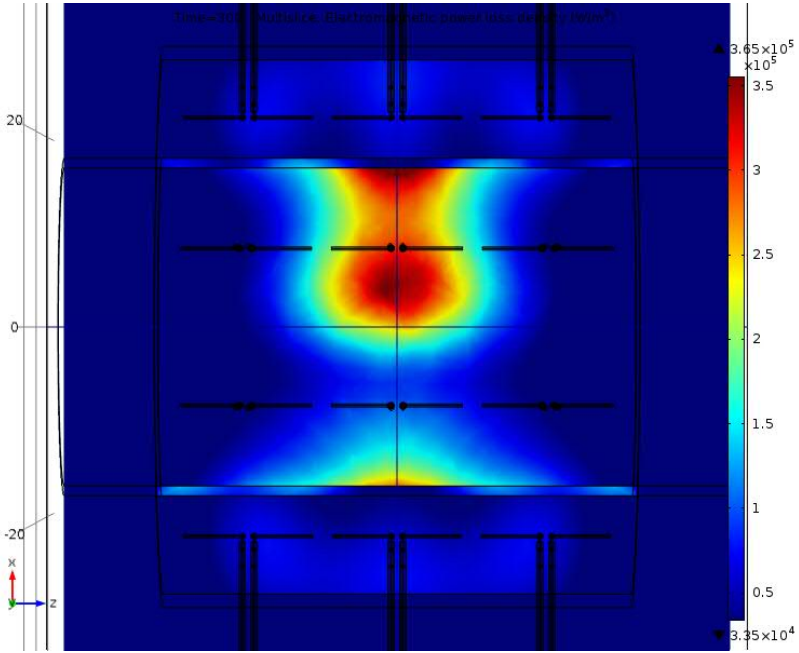


Coronal

175MHz 24 channel System
4cm Steering
Muscle Phantom, PG Bolus

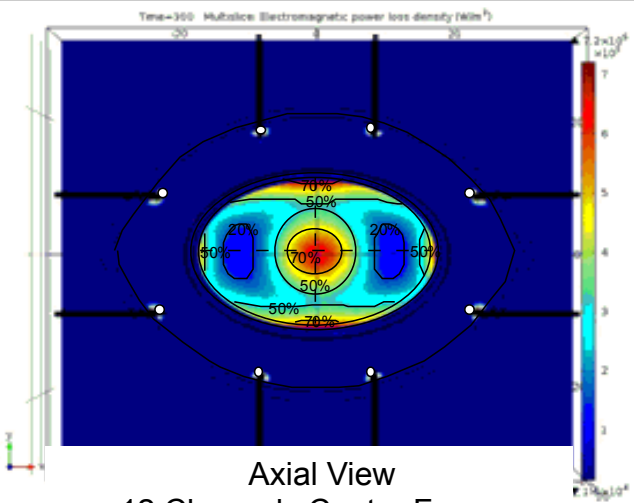


Axial



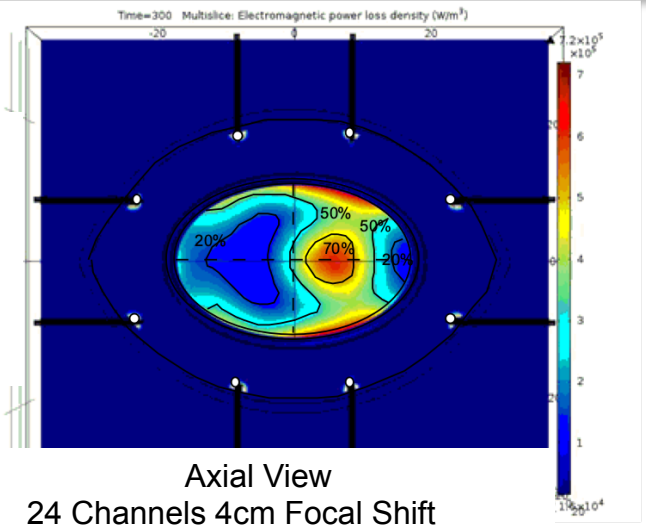
Coronal

175MHz 24 channel System
4cm Steering
Muscle Phantom & PG Bolus



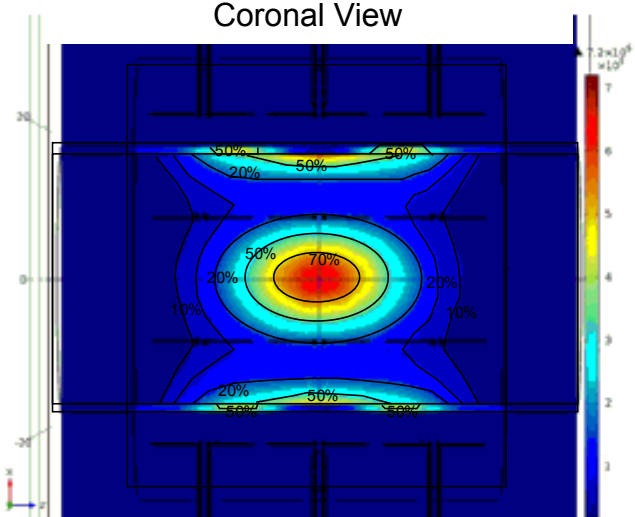
Axial View
12 Channels Center Focus

140MHz Sigma Eye
24 dipoles & 3 rings,
Water Bolus,
2/3rd Conductivity
Muscle Phantom
13.6x12.3x20.2cm,Vol=1,769cc

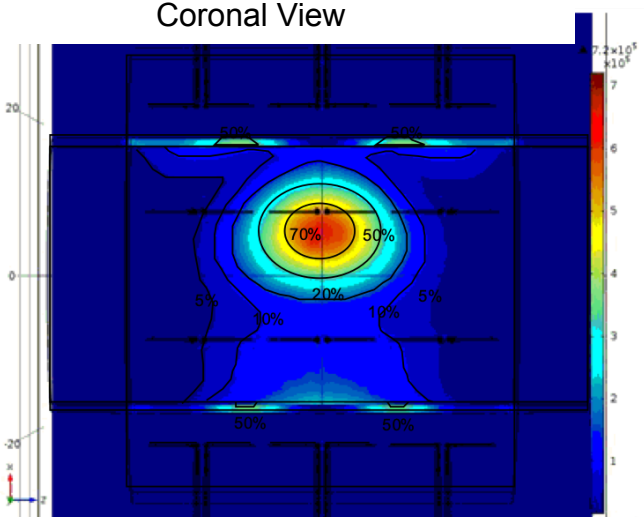


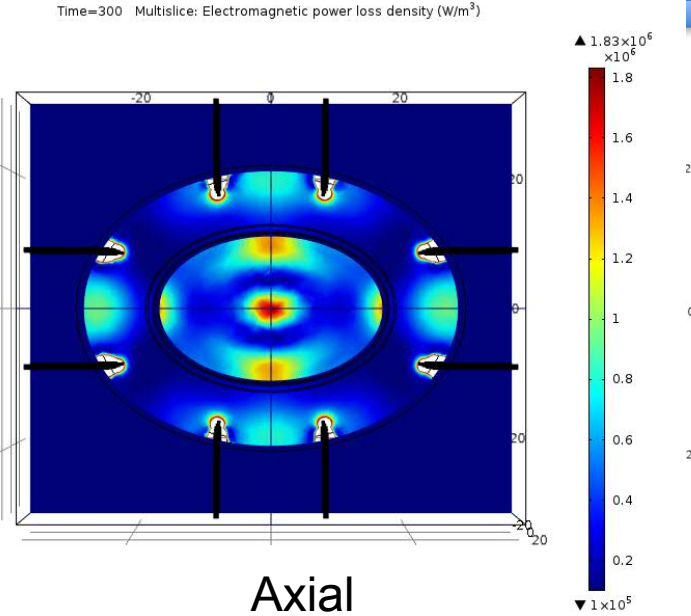
Axial View
24 Channels 4cm Focal Shift

Coronal View

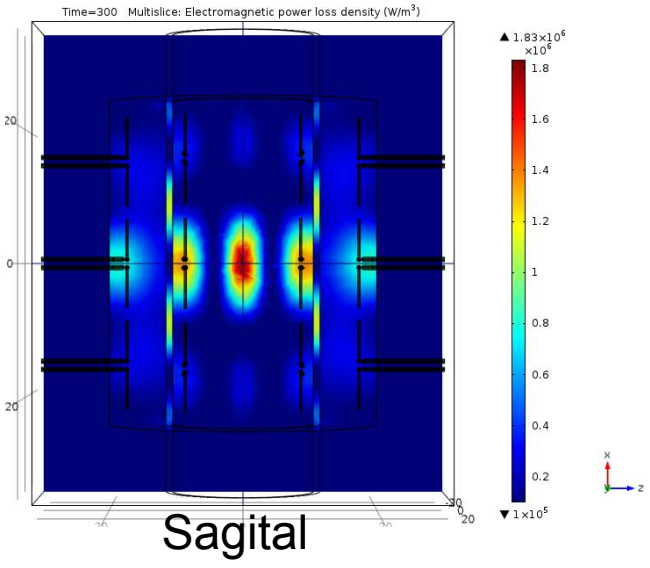


Coronal View

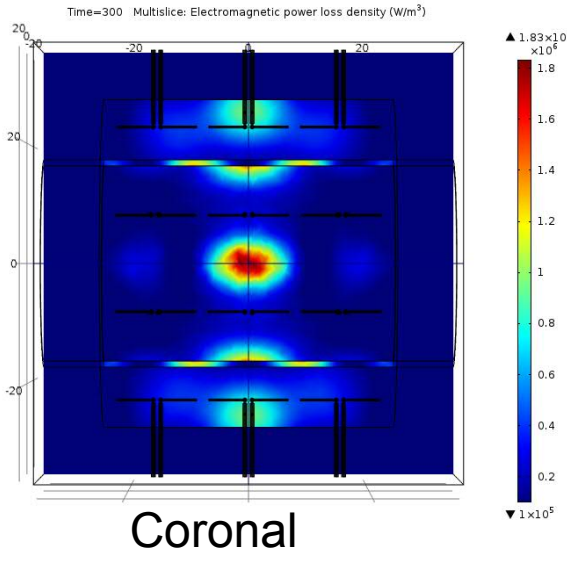




Axial



Sagital



Coronal

250MHz Elliptical SigmaEye, Saline Phantom,
Central 3D focus, PG Bolus
4.3x6.2x11.0cm, Vol.= 143cc.

RF vs HIFU Phased Array

	RF Phased Array	HIFU Phased Array
Focus	Large	Small
Focal Steering	Simple	Complex
Air & Bone	Tolerant	Blockage
Large Tumors	Suitable	Limited
Dose Monitoring	Easy	Difficult
SAR Pattern	Uniform	Non-Uniform

Future Clinical Applications

- Proton therapy with HT
- Renewed interest in Brachytherapy +HT
- Immune response with HT
- Brain targeted phased array treatments
- Superficial arrays for more uniform surface heating

Treatment Tools Being Planned

- Brain phased array Hal.o
- Advanced high frequency phased array
- MR guided focused thermal therapy
- Superficial arrays
- Further evolution of current systems
- Advancements in treatment planning