Temperature measurements during Oncothermia (Collection of temperature measurements in loco regional hyperthermia)

Dr. Oliver Szasz

Oncotherm GmbH, Germany

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(Collection of temperature measurements in loco regional hyperthermia)

The temperature is a permanent question of the hyperthermia applications in oncology. There are numerous discussions and debates about its importance and problems of its rising deeply inside of the human body. There are intensive discussions about its role in the treatment, looking for controlling parameters and well defined treatment goals of clinical oncologic hyperthermia. The doubts about temperature have multiple origins.

The arguments are sharply differing. The temperature supporters base their opinion on the higher blood-flow by temperature, which delivers more oxygen for complementary radiotherapy and increases the drug concentration and its metabolism in the tumor. The opposition refers on the higher nutrition support and increased metabolic rate of the tumor by growing blood-flow, as well as the higher risk of the malignant dissemination by intensive blood-circulation. The pro-group refers on the control of the treatment by a measurable parameter, while the con-group notes the natural delocalization (smearing) of the temperature from a local volume in a well conductive environment.

Compare the different methods is not a simple task. The energy delivery does various changes in the complex living system, which makes the methods incomparable by an only single parameter. The identical energy exposition does not mean same heating efficacy. The heating efficacy depends on the actual conditions [1], [2], and on the organ to be heated [3] as well as the chosen frequency. The temperature is used in most of the cases as a "success parameter" in hyperthermia, trying to equalize it and declare as a measurement of the energy absorption. The temperature shows only the average kinetic energy of the particles and units in the measured target, but it tells nothing about the chemical and structural changes there. However, the aim of the therapy is to reach structural and chemical changes to stop the malignant processes. The temperature is not enough to compare the methods, [4].

Nevertheless, the temperature and energy distribution is very different [5], it is not possible to fit the specific absorption rate (SAR) and the developed temperature. The amount of the energy losses deviate by the actual conditions, and by the fundamental law of nature, the temperature smears in the environment. Any proper focus serves as a heat-source to heat up its surroundings.
The debates are heated by increased interest for targeted therapies, for what the hyperthermia could be a potential candidate.

Oncothermia changes the paradigm. Oncothermia technology heats non-equally; concentrating the absorbed energy to the intercellular electrolytes [6]. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis. The synergy of electric field with the thermal effects potently and selectively does the job [7].

The applied power and the reached temperature are far not proportional. Despite of the longer time (by ~26%), larger forwarded power (by ~8%) the increased temperature is less (by ~12%) in the second time. It is not because the energy conservation is hurt, but due to the cooling which was applied (and not registered) during the treatment to prevent the skin from burn. We know it well, that the blistering threshold of heating power going through the human skin is ~0.45W when it is pumped during an hour [8], so the cooling was always fit for the safe use. The extra power was conducted away by the surface cooling. It is a patented technical trick of Oncotherm how to make

the surface cooling well, and using most of the energy for the heating of the tumor without loosing it by the active cooling.

This is why oncothermia, (using the same blistering threshold) can reach higher temperatures. We recapitulate those results to clear the differences: oncothermia treatment had $\sim6^{o}$C temperature increase with ~70 W during 60 min in the human sarcoma [9] and reaching 44 ^{o}C with 120 W in case of mammary tumor [10]. In veterinarian application, where the blistering threshold was of course higher in the anesthetized animal and the heated volume was much smaller than in human cases, the temperature increase was $\sim14^{o}$C with ~25 W during 30 min [11].

The only point for these results is to keep the energy for the job, and not waste it for various energy factors in the electronic solution, in the filed emission (radiation), in the surface physiology or in the electrode construction. Despite of the fact, that Oncotherm is reaching his extremely good results by the electric field (which was directly shown clearly in "galvano" treatment), the temperature conditions are also present and necessary. This is well shown in the synergy of the temperature and field effects [12].

Below I will show our systematic proofs on the selective temperature developments, our high-scale temperature measurements and proofs of oncothermia as a definite improvement of oncologic hyperthermia. Oncothermia is such kind of oncologic hyperthermia, which together with the better efficacy, safer and controllable than other heating methods.

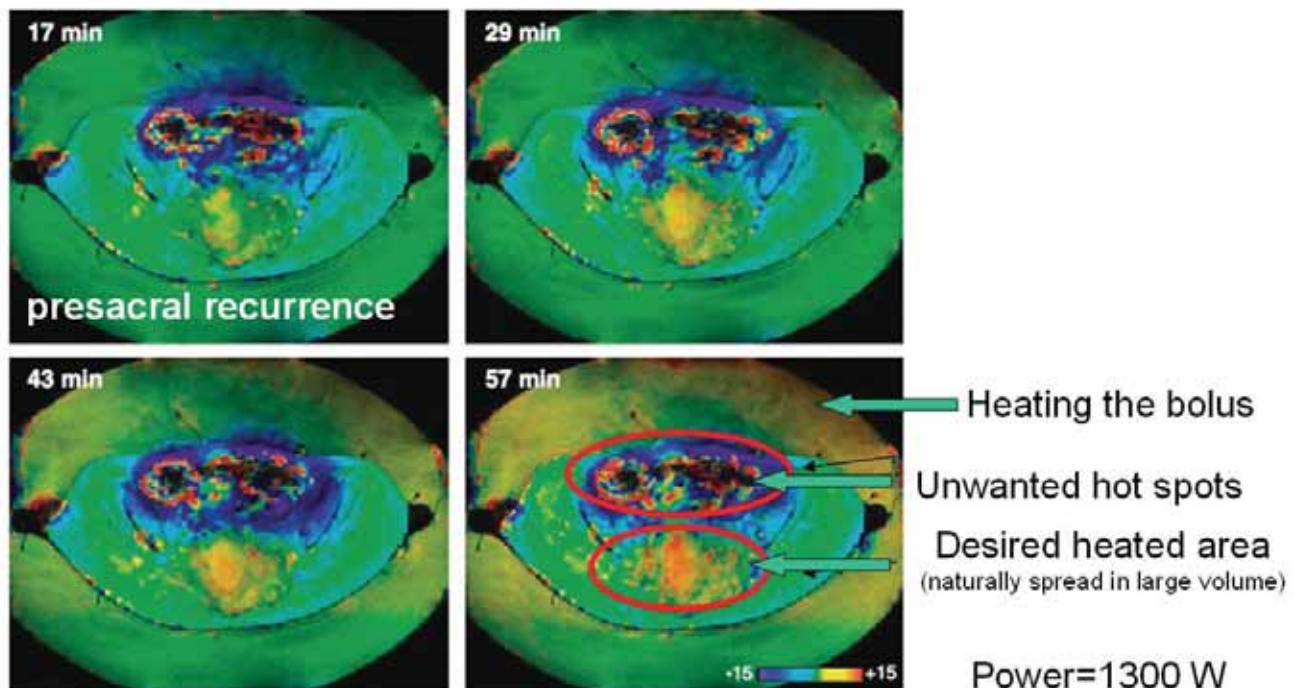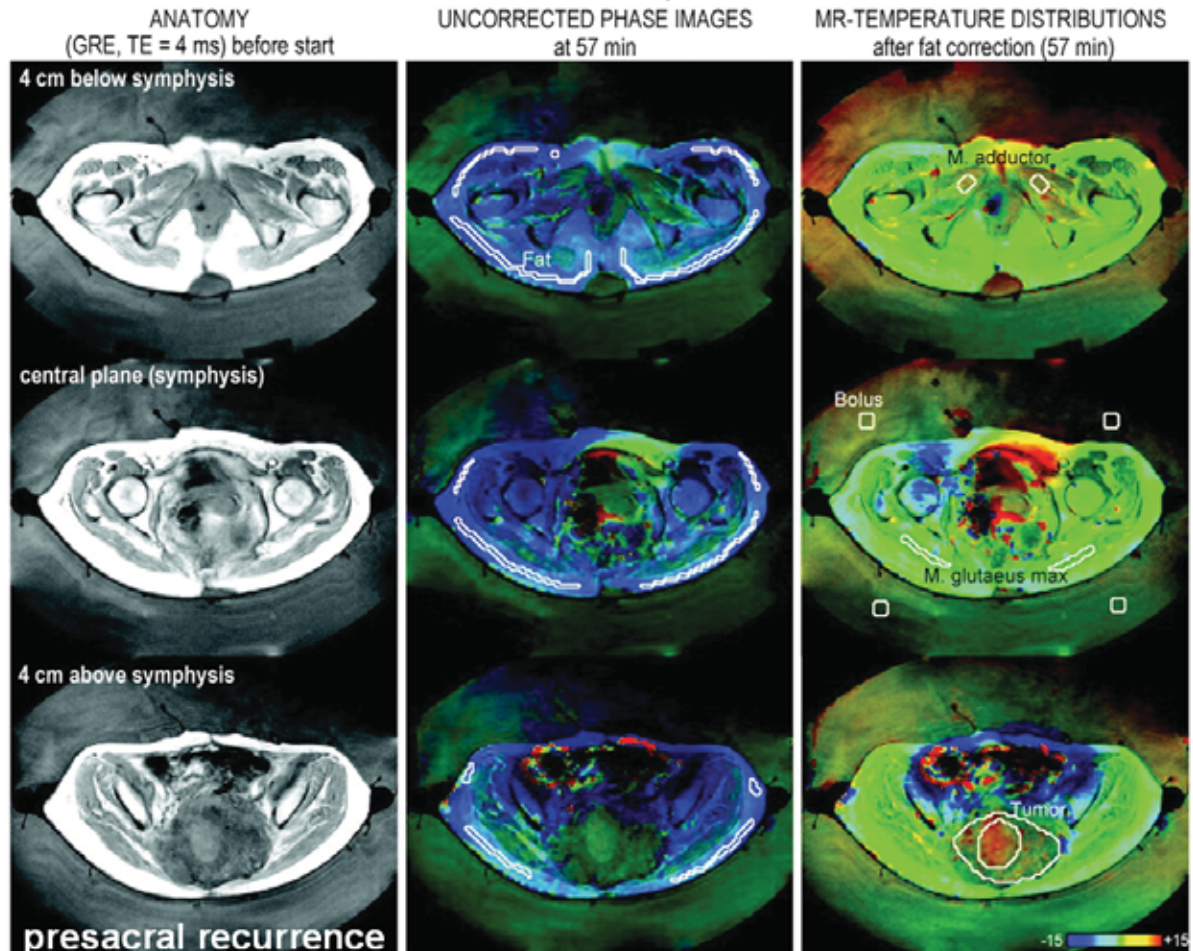## *Temperature measurement for BSD device*

This device is a radiative heating system, having antenna-array around the body. The published data show non-invasive temperature measurement (by MRI sensing and calculation from the T1 and T2 time-shifts). Results show a problematic focusing (having many hot-spots) as well as the smearing of the temperature by time.

In case of radiative applications the situation is not better. The temperature elevation in the tumor after 57 min was 4.2 ^{o}C; reached by as high power as 1300 W [13]. The overall heating is obviously shown with some characteristic (unwanted) hot-spots. The elapsed time smears the relative focused temperature. The temperature increase in the tumor was in average 4.2 ^{o}C, while in the surrounding muscle 3.8 ^{o}C **[13]**. Is this the focus, which we expected?
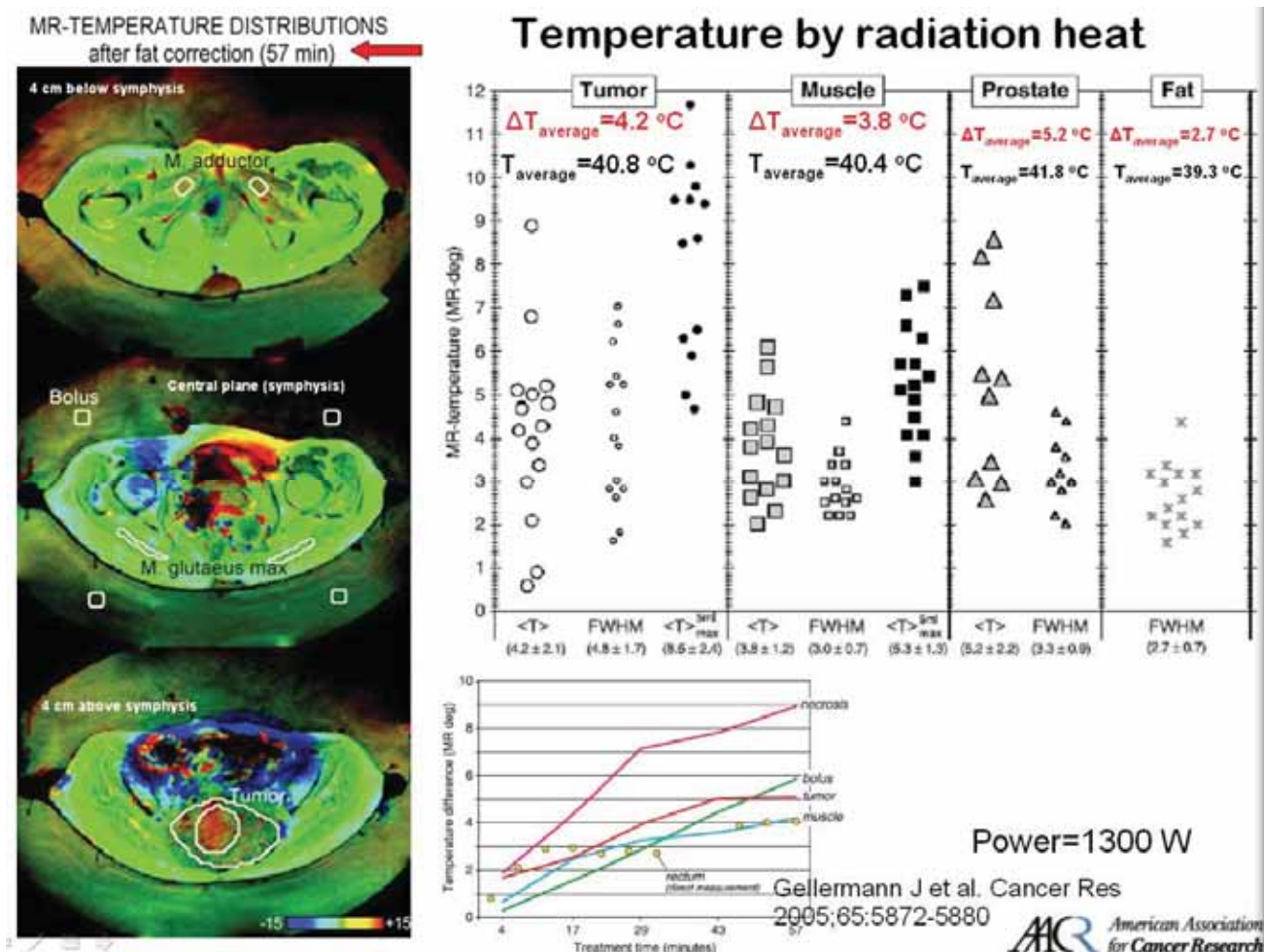
Temperature by BSD devices

Gellermann J et al. Cancer Res 2005;65:5872-5880
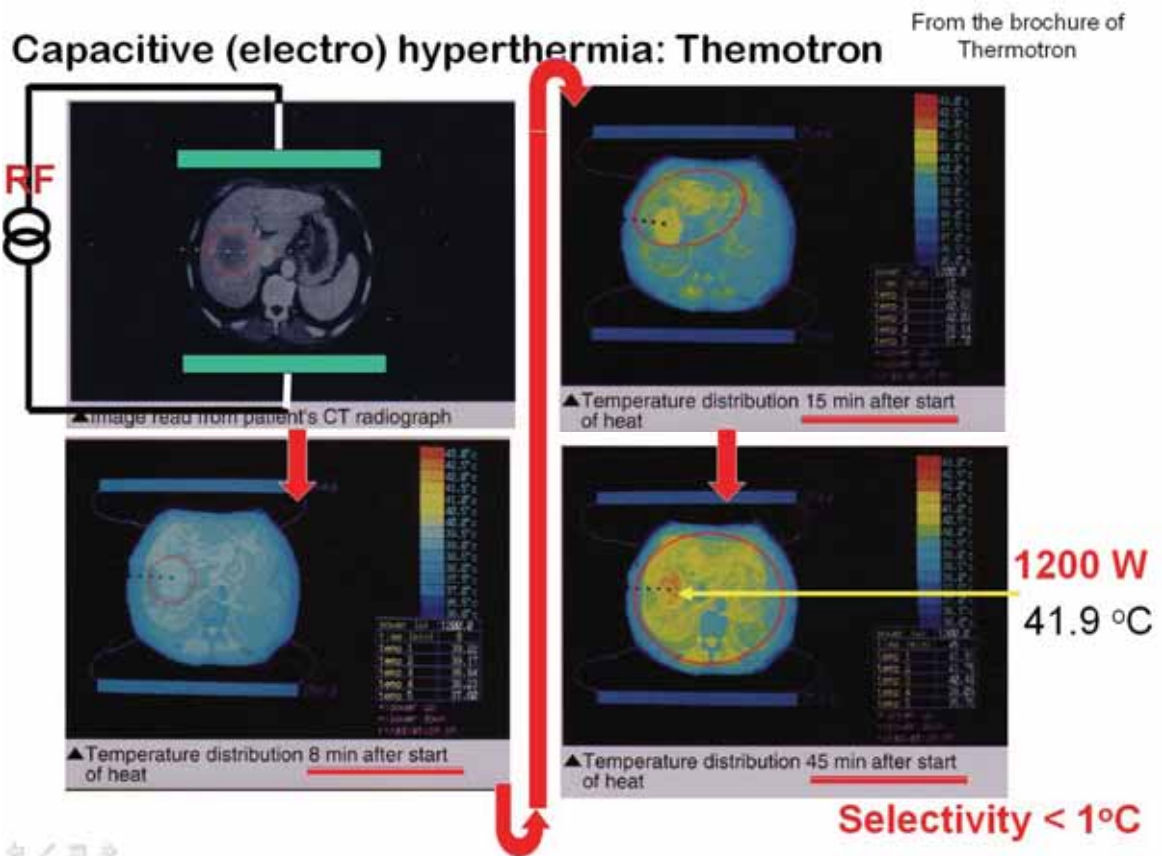
American Association

ANATOMY
(GRE, TE = 4 ms) before start

UNCORRECTED PHASE IMAGES
at 57 min

MR-TEMPERATURE DISTRIBUTIONS
after fat correction (57 min)

Heating the bolus

Unwanted hot spots

Desired heated area
(naturally spread in large volume)

Power=1300 W

Selectivity < 0.5°C

MR-TEMPERATURE DISTRIBUTIONS after fat correction (57 min)

Temperature by radiation heat

Gellermann J et al. Cancer Res 2005;65:5872-5880

Power=1300 W

American Association for Cancer Research

The few centigrade increase of the temperature by 1300 W energy shows how much mass is heated instead to concentrate on the tumor. To see the power capacity, we compare the electric heating for tea-making. A standard speedy Electric Tea Kettle uses 1500 W to boil two cups of water within two minutes. The increase of the temperature for the ~ 0.5 liter water is ~75 ºC. The electric power is very effective to change the temperature when it is focused to do so. The electromagnetic radiation increases the tumor temperature by 3.2 ºC, while the intensively cooled, large volume water-bolus had a higher increasing (5.8 ºC) with pretty linear growth slope.

Thermotron device

The Thermotron is a capacitive coupled device, using the electro-hyperthermia technique (no modulation is applied). The same problems as for BSD (except the hot-spots) could be realized in this case as well. A typical capacitive coupling solution pumps enormous energy, exceeding 1 kW. The rise of temperature after 45 min was 4.8 ºC but the reached focus does not differ greatly in its temperature from its overall neighborhood [14].The focus, however, is not effective. The temperature is distributed by time.

Capacitive (electro) hyperthermia: Themotron

RF

▲Image read from patient's CT radiograph

▲Temperature distribution 15 min after start of heat

▲Temperature distribution 8 min after start of heat

▲Temperature distribution 45 min after start of heat

1200 W
41.9 °C

Selectivity < 1°C

Heating by 1200 W

Source: brochure of Thermotron

Power: 1200 W (Thermotron)

Legend:
- T (tumor centre) [C]
- T (tumor perifery) [C]
- T (tumor sorrounding) [C]
- T (healthy) [C]
- T (skin surface) [C]

Tumor temperature — T=41.8 °C
Tumor vicinity temperature — T=40.5 °C
Healthy surrounding temperature — T=39.9 °C
Skin temperature — T=35.8 °C

Temperature [C] vs Heating time [min]
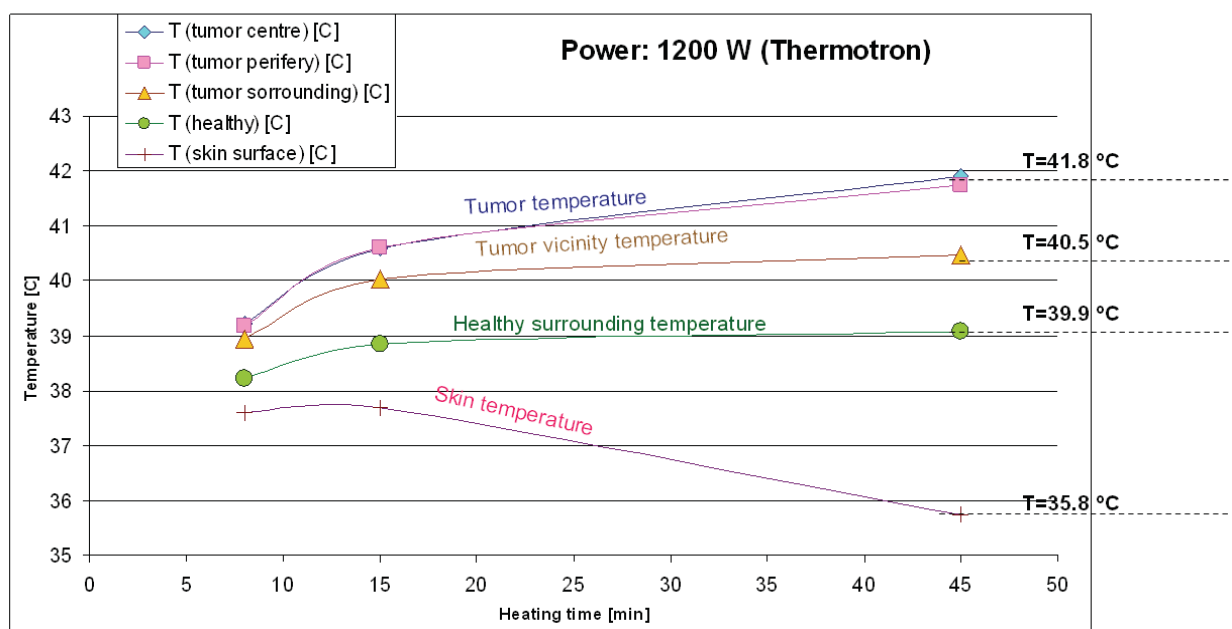
Subcutaneous and deep tumor temperature (Thermotron RF-8)
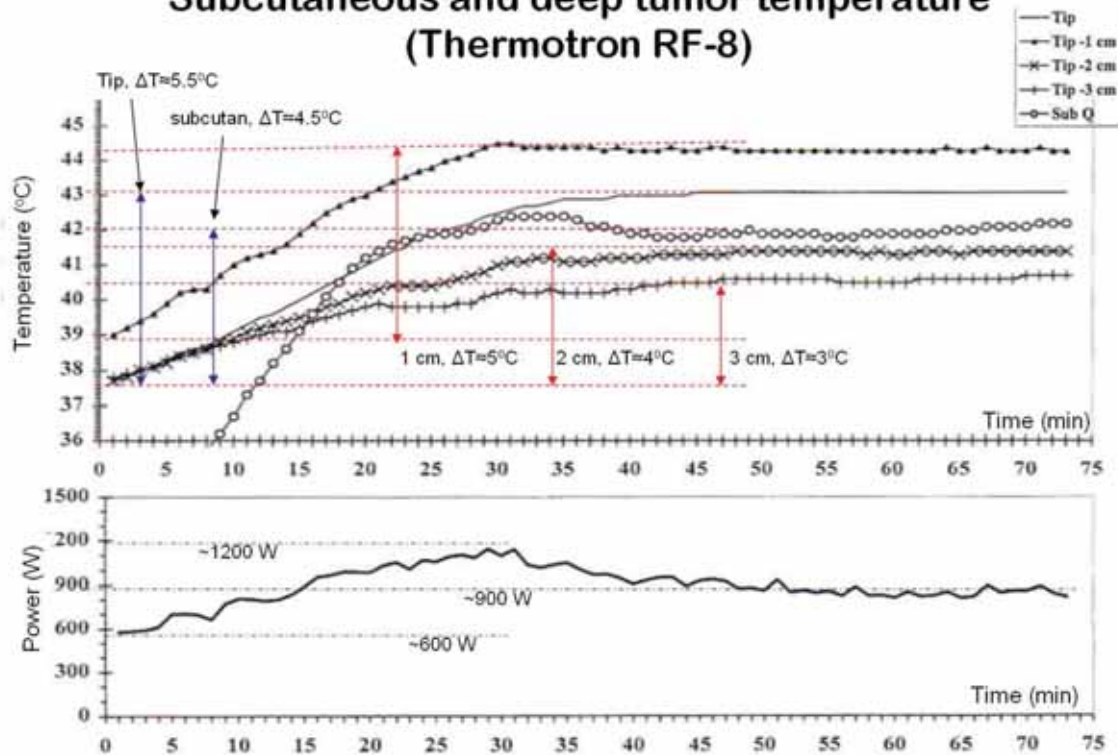
PH Sugarbaker, et.al.: Radiofrequency Hyperthermia Alone in the…, M. Kosaka: Thermotherapy for Neoplasia, Inflammation, and Pain, Springer-Verlag Tokyo 2001, pp. 458

The physiological feedback regulates the local temperature, which acts also against the local heating.

The temperature is physiologically regulated

Katsuyuki K (1994) Thermotherapy in the treatment of locally advanced non-small cell lung cancer Int. J. Rad.Oncol. Biol. Phys. 30(5):1171-1177
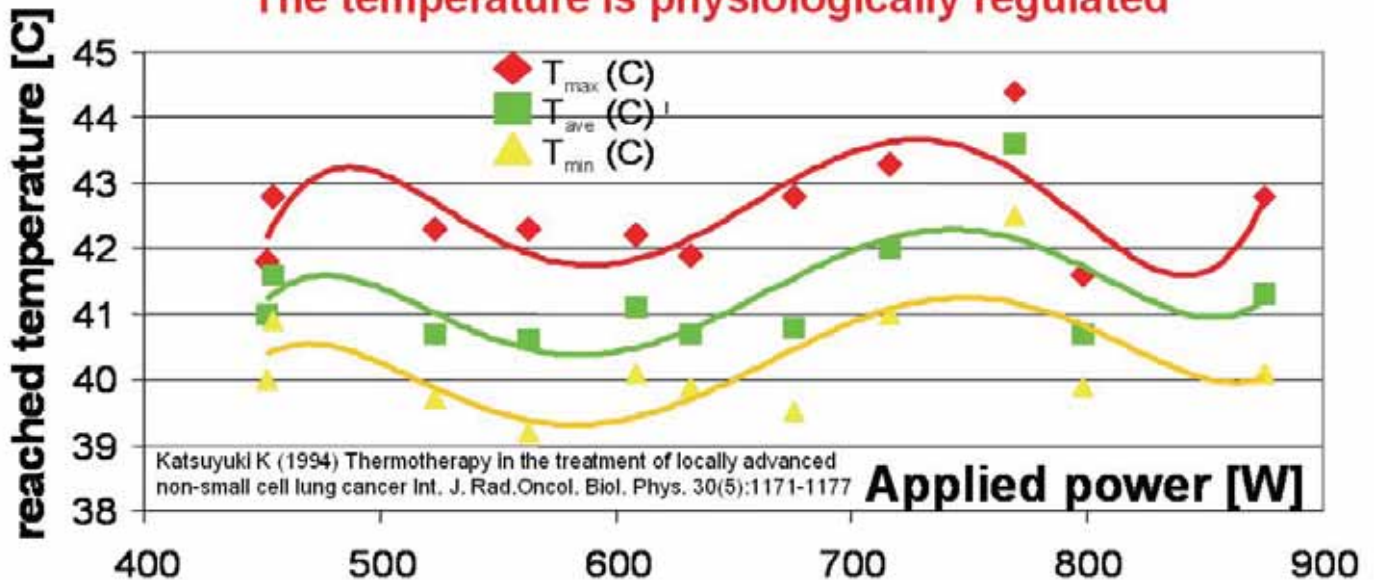
Dutch device (Rotterdam)

Dr. van der Zee had shown clearly the problem of the difference between the absorbed energy and the developed temperature. When the blood-flow is high, the temperature remains low despite of the extreme energy absorption, and vice versa, the low energy can heat the volume where the blood does not cools intensively. Nevertheless, the temperature and energy distribution is very different [15], it is not possible to fit the specific absorption rate (SAR) and the developed temperature. The amount of the energy losses deviate by the actual conditions, and by the

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fundamental law of nature, the temperature smears in the environment. Any proper focus serves as a heat-source to heat up its surroundings.

Energy and temperature are not the same!

CT scan

Energy distribution

Temperature distribution
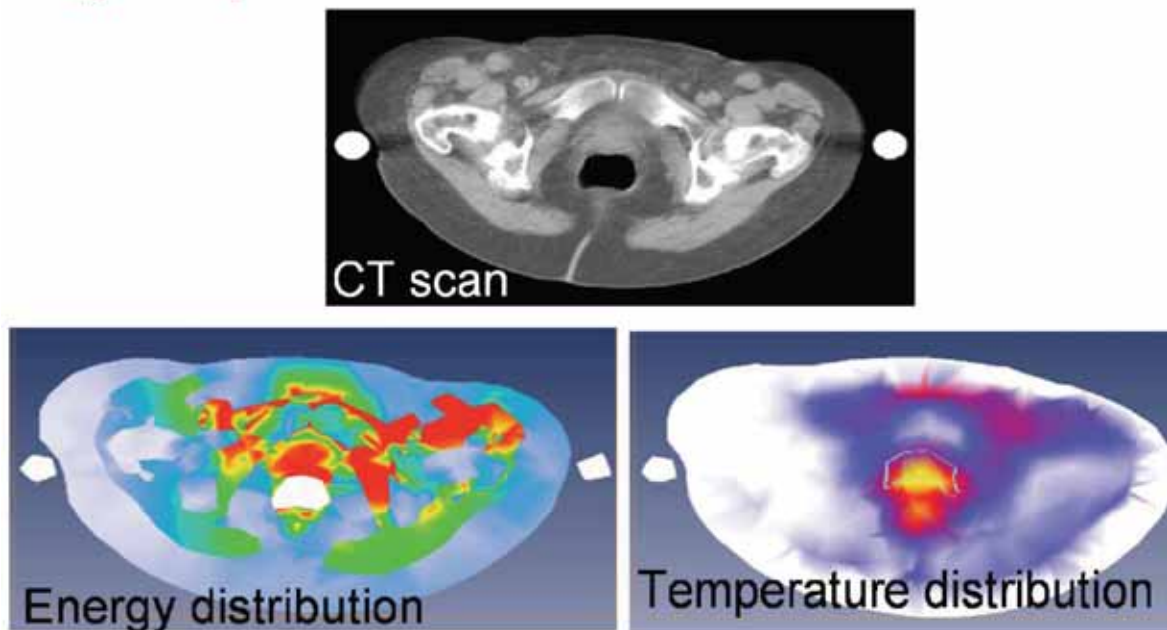
J.Van der Zee: ICHS, Mumbai, 2005

Erasmus MC

Oncotherm measurements

I would like to show various experimental and clinical temperature measurements without comments, only for the documentation.

Model systems

Comparison of bolus and textile electrodes on saline (100W)
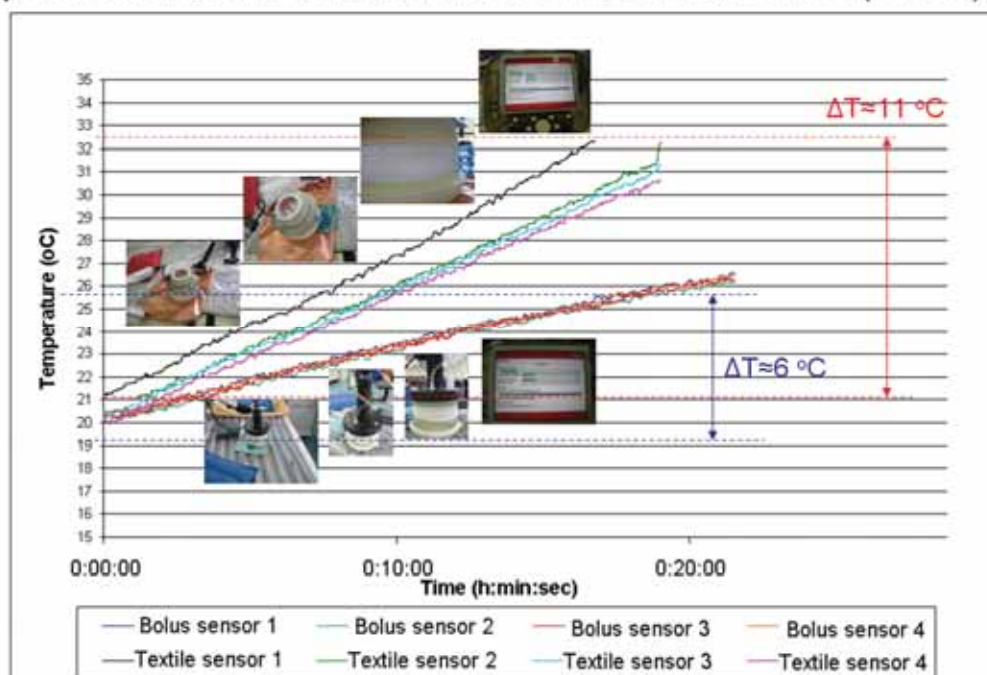
Presentation of the capacitive heat delivery

Egg experiment
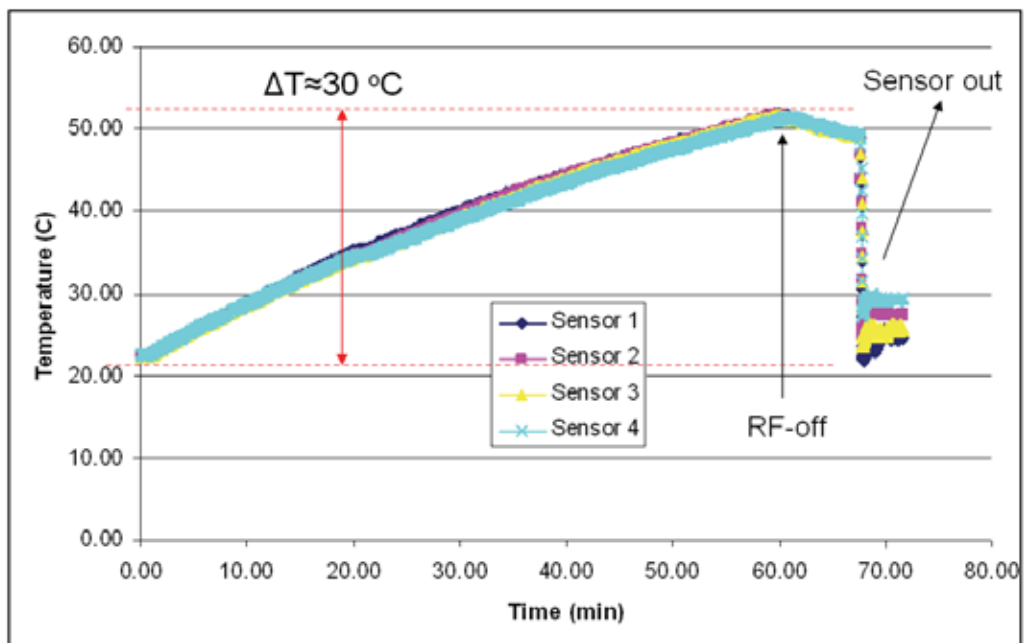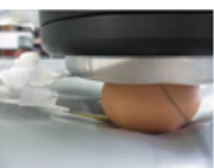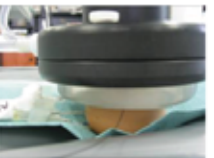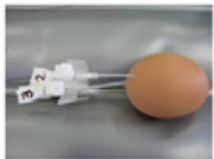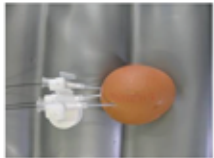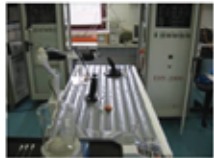
Early experiment with bolus in that time (~1993)
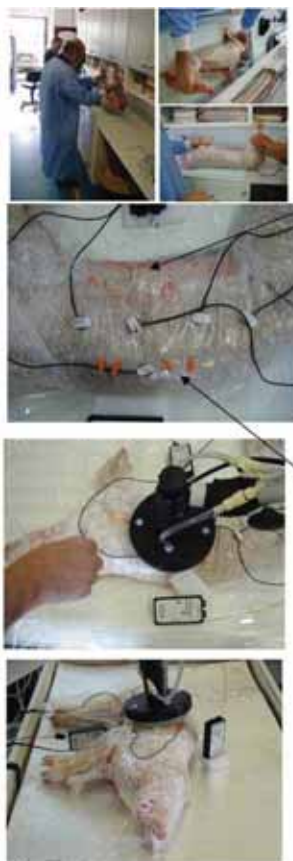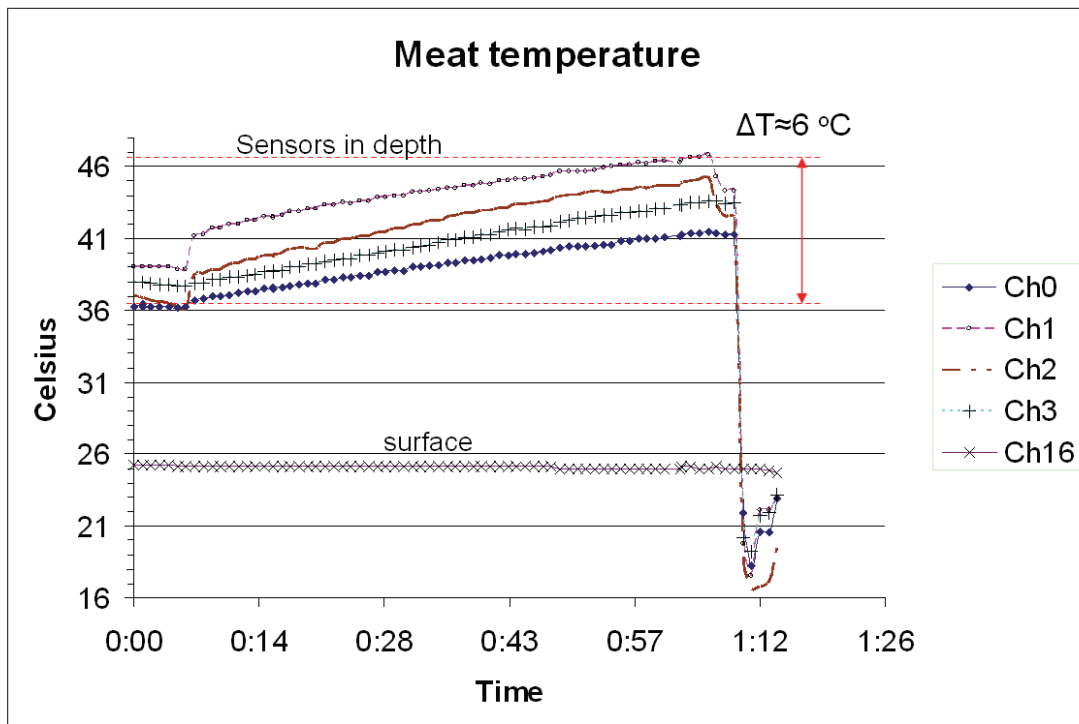
Meat temperature

Piglet experiment power on/off (~2001)
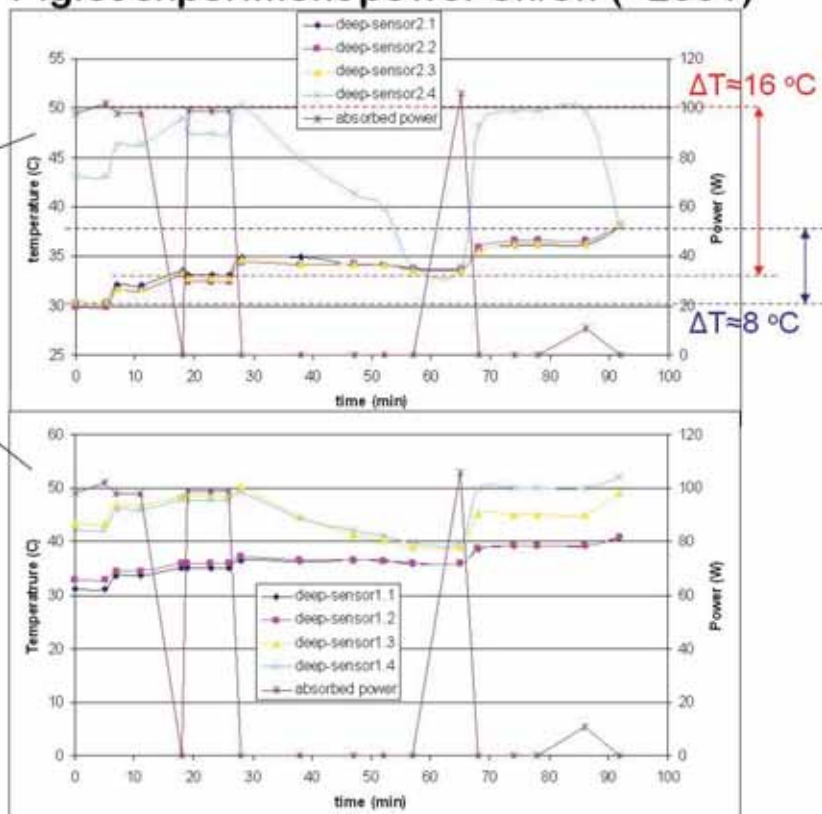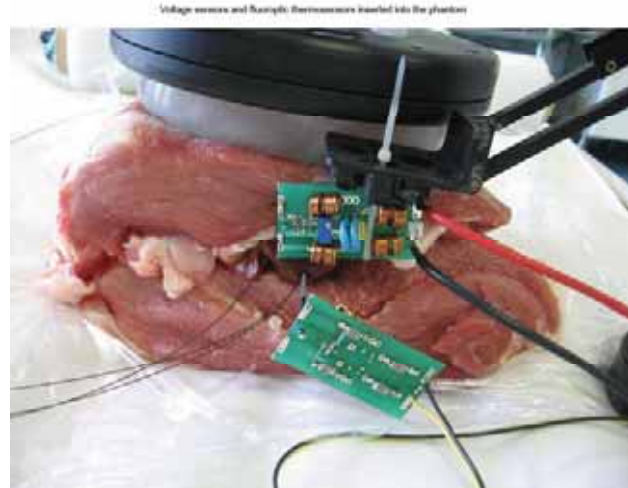
Temperature [C]
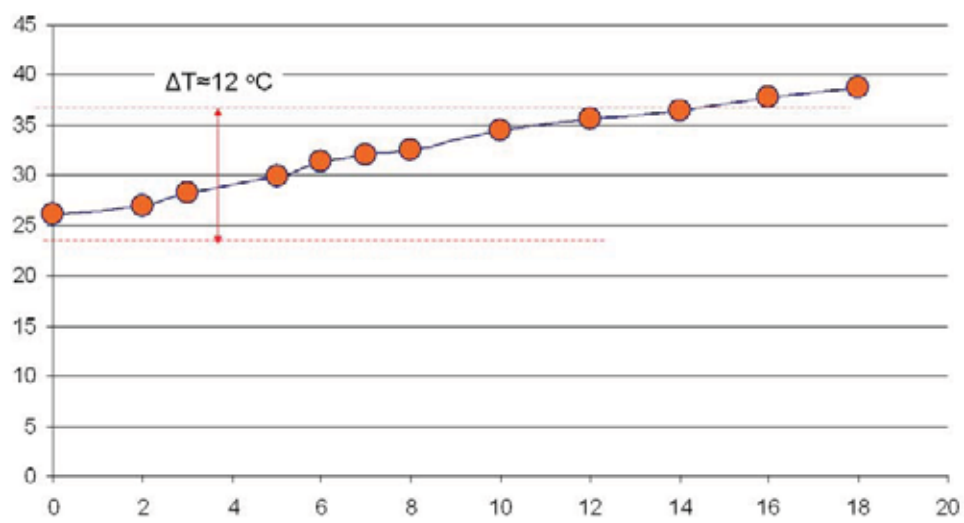
Deep heating of the rib/liver model (Prof.Herzog, Fachklinik Dr. Herzog, Publsihed in Forum Hyperthermie)

Lokale Hyperthermie am Modell

Meßwerte: Leberoberfläche: ΔT = Temperaturanstieg °C / 15 min

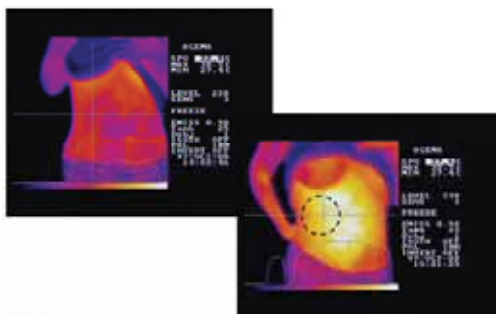**Bedingungen:**
20 cm Applikator
100 W Leistungsaufnahme 15 min
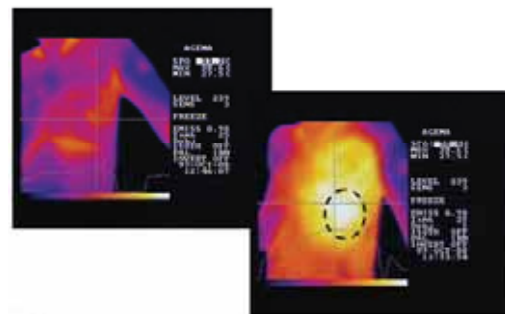(Leistungsabgabe 105W)

Ablauf:
Gute Kopplung
Minimale Reflexion

Zusammenfassung: Messungen mittlerer Applikator (20 cm); 15 min mit 100 W

ΔT Haut	5,4° C (2,6° – 7,1° C)
ΔT Leber-Oberfläche	4,1° C (2,6° - 3,9° C)
ΔT Lebertiefe	2,4 – 3,9° C

Lokale Hyperthermie am Modell

Meßwerte: Leberoberfläche: ΔT = Temperaturanstieg °C / 15 min

Bedingungen:
20 cm Applikator
100 W Leistungsaufnahme 15 min
(Leistungsabgabe 105W)

Ablauf:
Gute Kopplung
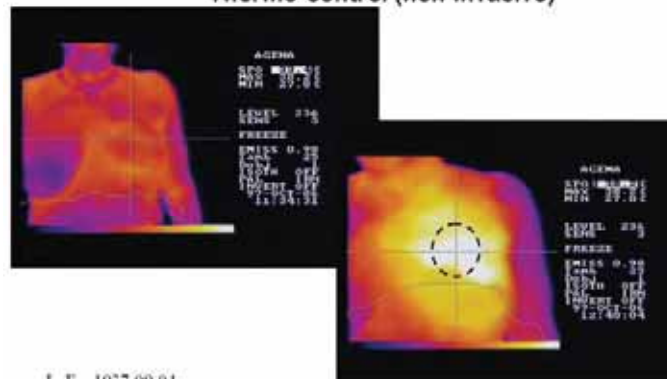Minimale Reflexion

Thermo-camera control

Thermo-control (non-invasive)

Thermo-control (non-invasive)

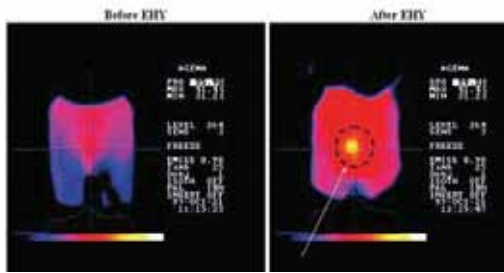**Thermo-control (non-invasive)**

L. F. 1937-09-04

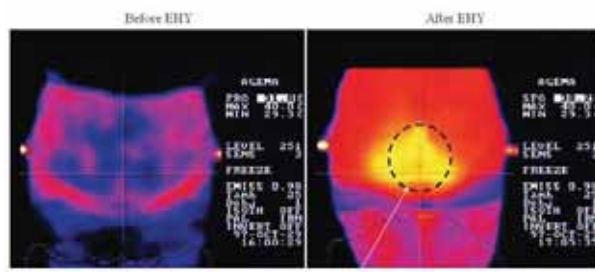Tumammael.s.pleuralomet. ; carcinoma planocellulare interductale
chemotherapy, radiotherapy,

Thermo-control (non-invasive)
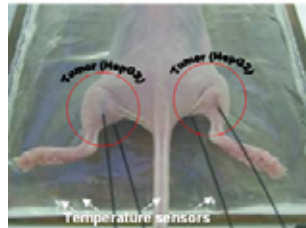G.F. 1930-10-14 (F)
Diagnosis: rectum carcinoma

Before EHY   After EHY

Thermo-control (non-invasive)
F.L.K. 1949-12-12 (F)
Diagnose: myoma uteri l.s.
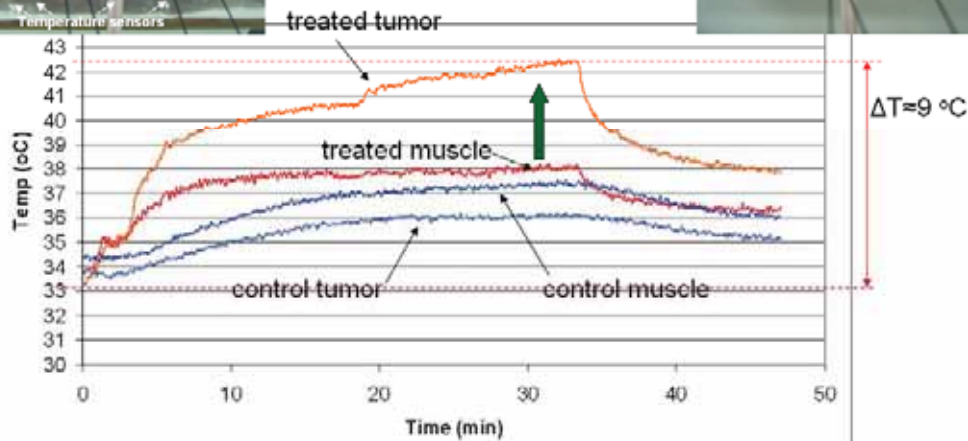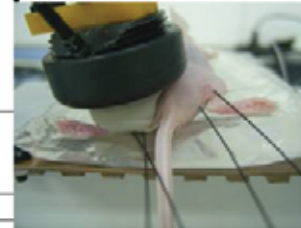
Before EHY   After EHY

Selective macroscopic energy deposition

Human hepataocellular carcinoma (HEPG2) study

Temperature measurment

treated tumor

treated muscle

control tumor   control muscle

$\Delta T \approx 9\ ^{\circ}C$

Oncothermia method can selectively heat the tumor!

Invasive optical temperature measurement

Andocz G. PhD. Thesis. 2006

Measurement setup

$\Delta T \approx 6\ ^{\circ}C$

7W/1.4W, 42 min (SWR=1.5)
[17.6 kJ /3.5 kJ]

$\Delta T \approx 10\ ^{\circ}C$

20W/4.7W, 5 min (SWR=1.6)
6 kJ /1.4 kJ

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Invasive optical temperature measurement

(Experimental animal: healthy female Beagle dog, (3 years old, 10kg bodyweight)

ΔT≈10 °C

Incident 50W (150 kJ), absorbed: 36 W (108 kJ), 50 min (SWR=1.8)

Dr.Andocs G: 2005
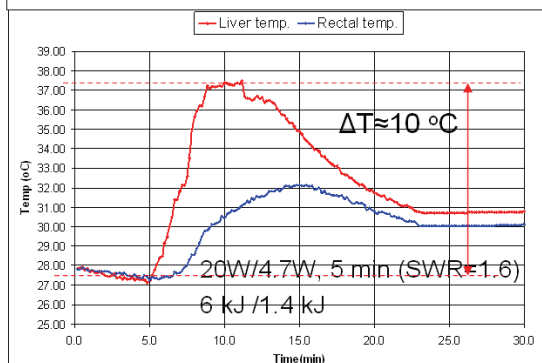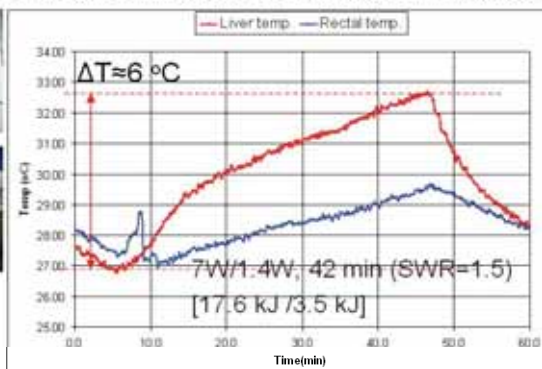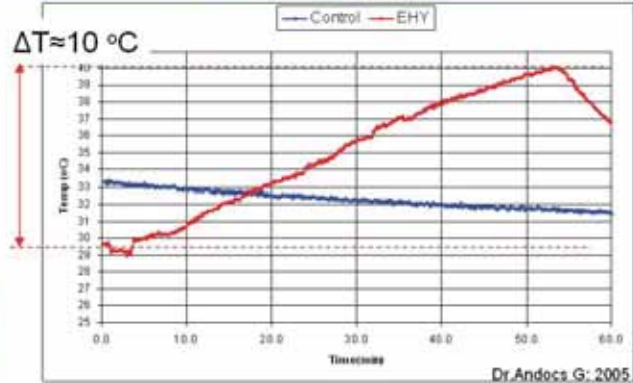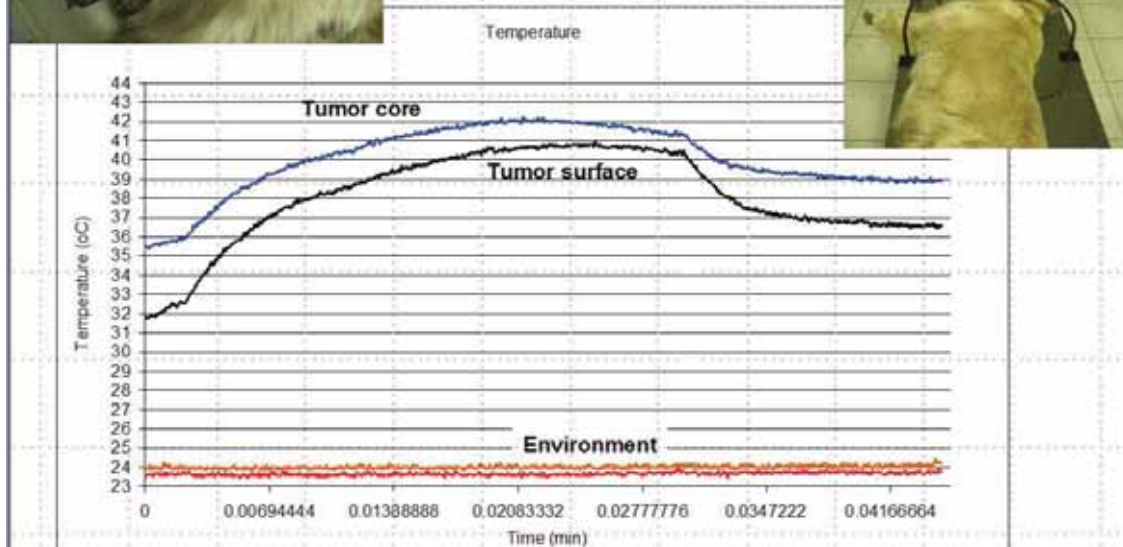
Invasive remote temperature tests

Test animal: healthy Beagle dog
Power: 20W/16W (SWR:1.5)
Energy: 36 kJ/28.5 kJ
Treatment duration: 30 minutes
Temperature sensor: placed subcutaneously under the electrode
Temperature measurement: every 5 minutes (RF switched off)

ΔT≈14 °C
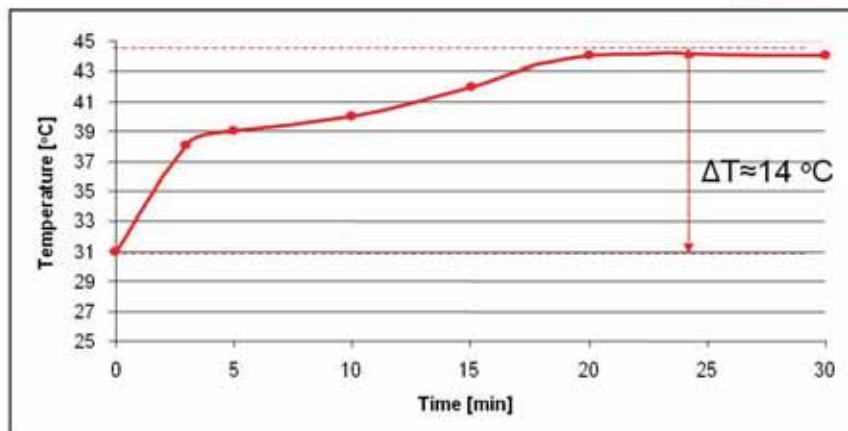
Dr.Andocs G: 2005

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Oral cancer temperature

Temperature

Tumor core
Tumor surface
Environment

Temperature (oC) / Time (min)

Scintiography study

Hypertermia   Control

0   20cm

Treated joint: Control joint:
76984/638=120,7/pix   65912/638=103,3/pix

Aim of the study: investigating the effect of hyperthermia to bone tissue – monitoring the radiopharmacon(^{99m}Tc-MDP) uptake of the hyperthermized knee joint
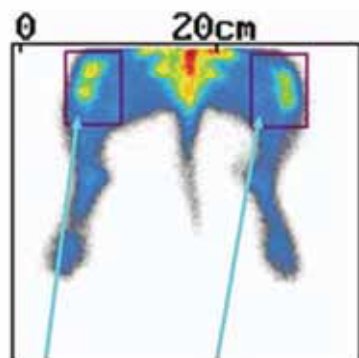
Test animal: healthly Beagle dog

Power: 30W (SWR:1.5) [54 kJ]

Treatment duration: 30 min

Radiopharmaceutical: 400 MBq ^{99m}Tc-MDP

Scintigraphy: 1 hour after the intravenous injection of radiopharmacon at the end of 30 min hyperthermia treatment
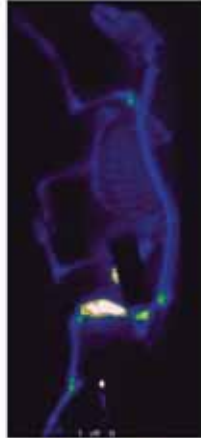
Scintigraphy: 1 hour after the intravenous injection of radiopharmacon at the end of 30 min oncothermia treatment

Oncothermia raised the bone-specific radiopharmacon uptake in the treated knee-joint by 17%.

OSTEOSARCOMA (DOG, dorka, 2007.01.18-29.)

Diagnosis: osteosarcoma
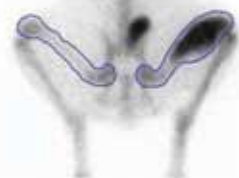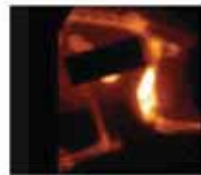

Before oncothermia 2007.01.09

ROI (total count):
Healthy femur: 26612
Tumoral femur: 238246
Tumor/healthy ratio: **8.95**

After oncothermia 2007.02.05

ROI (total count):
Healthy femur: 33433
Tumoral femur: 183625
Tumor/healthy ratio: **5.49**

Oncothermia decreased the intake of the radiopharmacon by 40% !

Preparation of temperature measurement in bull-terrier
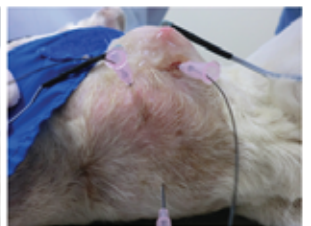
Tumor temperature in bull-terrier

Temperature

Intratumoral temperature measurement using invasive fluoroptic temperature measurement sensors, 12 years old bullterrier, recidival epithelial cell carcinoma in the lower neck region, oncothermia (10W)
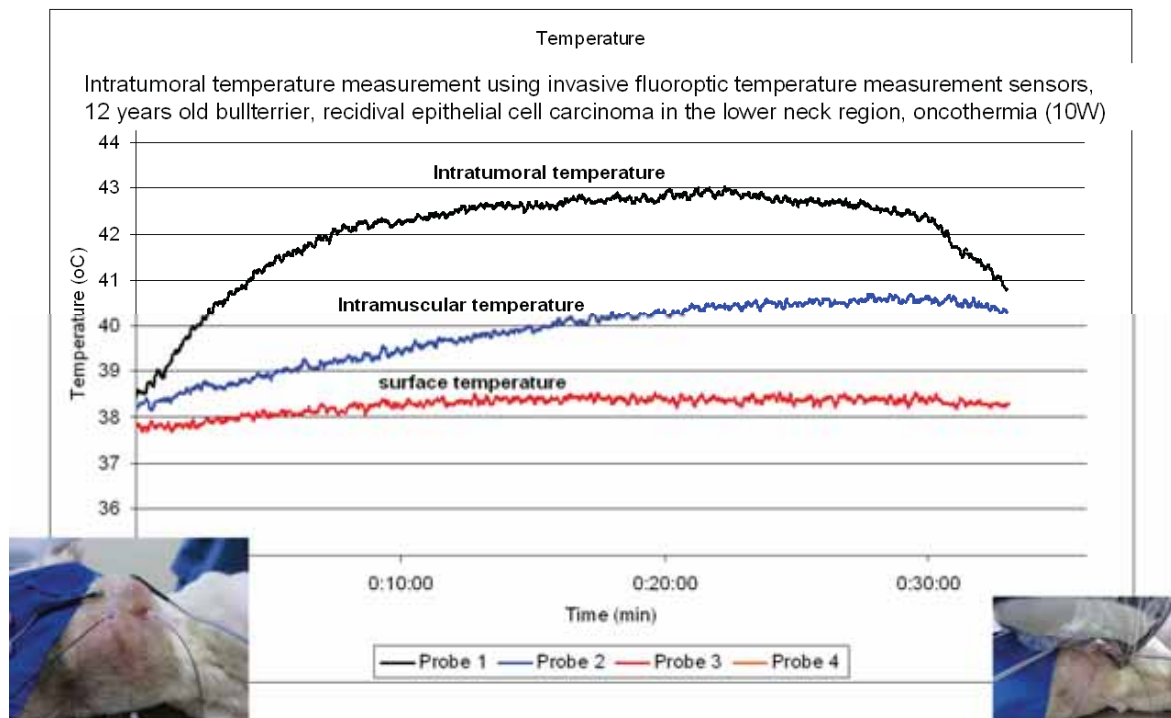
Human measurements (by chronology)

Invasive temperature measurement in CUP adeno CA

St. Elizabeth Hospital, Recklinghausen, 1998

Thermo-control (invasive)

St. Georg Klinik, Bad Aibling, 2000

Patient: Se.
Diagnose: Leber-Ca.
Therapiekombination: Tiefen-Hyperthermie
Messung vom: 29.12.2000
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C

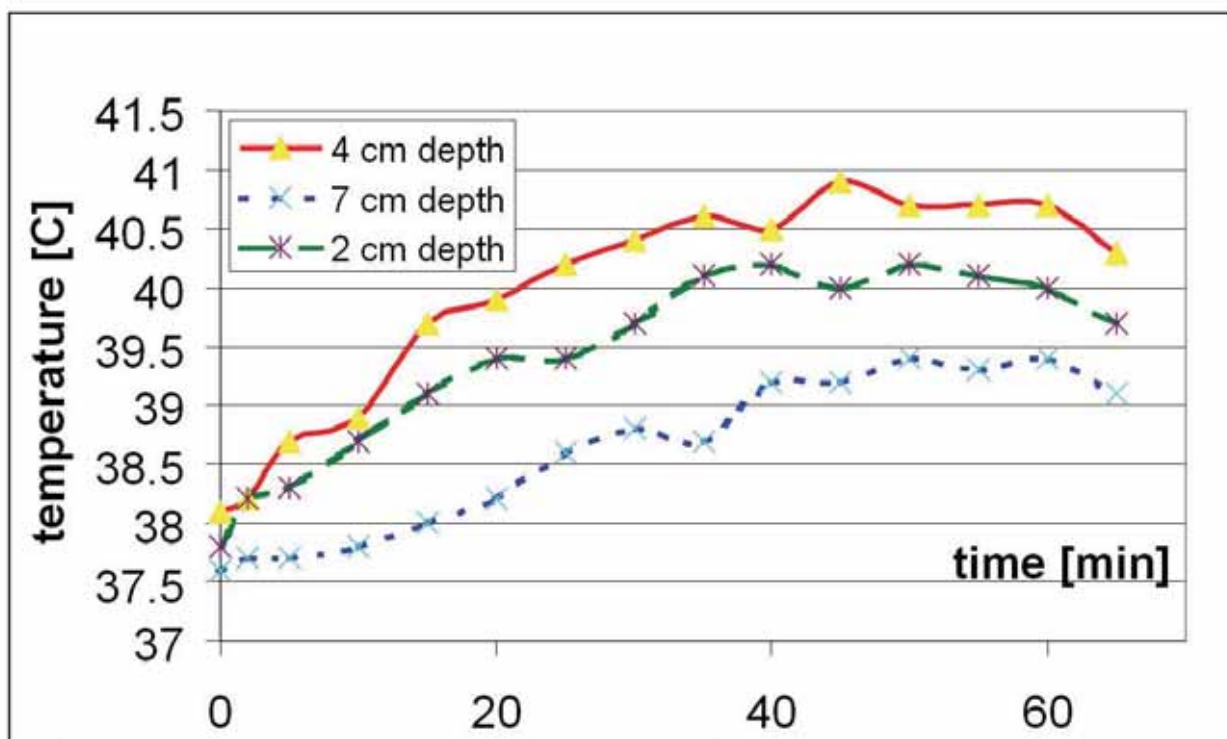**Temperaturverlaufsprotokoll**

- – • – Leistungsabgabe
- – ■ – Leistungsaufnahme
- – ▲ – Temperaturanzeige
- • • • Kanal 1 nicht im Tumor
- – × – Kanal 2 im Tumor
- – ■ – Kanal 3 Oberflächenmessung
- – ■ – Kanal 4 Oberflächenmessung

Anmerkung: Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.

Thermo-control (invasive)

St. Georg Klinik, Bad Aibling, 2001

Patientin: W.
Diagnose: Mamma-Ca.
Therapiekombination: Oberflächen-Hyperthermie
Messung vom: 04.01.2001
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C

Temperaturverlaufsprotokoll

- – • – Leistungsabgabe
- – ■ – Leistungsaufnahme
- – ▲ – Temperaturanzeige
- – • – Kanal 1 nicht im Tumor
- – ■ – Kanal 3 Oberflächenmessung
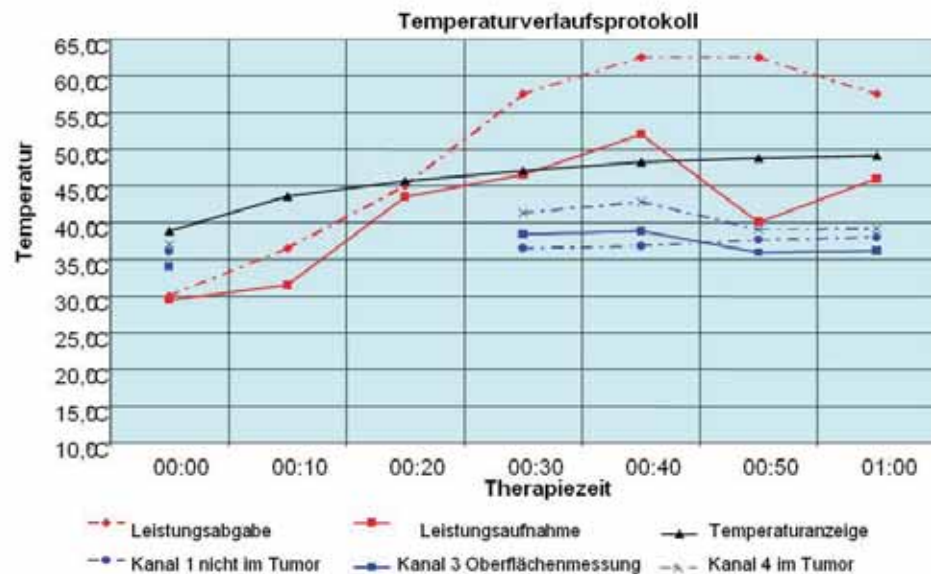- – × – Kanal 4 im Tumor

Anmerkung: Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.

Thermo-control (invasive)

St. Georg Klinik, Bad Aibling, 2001

Patientin: K., geb. 29.12.1940
Therapiekombination: Oberflächen-Hyperthermie und Chemotherapie (Cisplatin)
Messung vom: 04.01.2001
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C

Temperaturverlaufsprotokoll

−◆− Leistungsabgabe   −■− Leistungsaufnahme   −▲− Temperaturanzeige   −×− Kanal 1 im Tumor   −■− Kanal 4 Oberflächenmessung
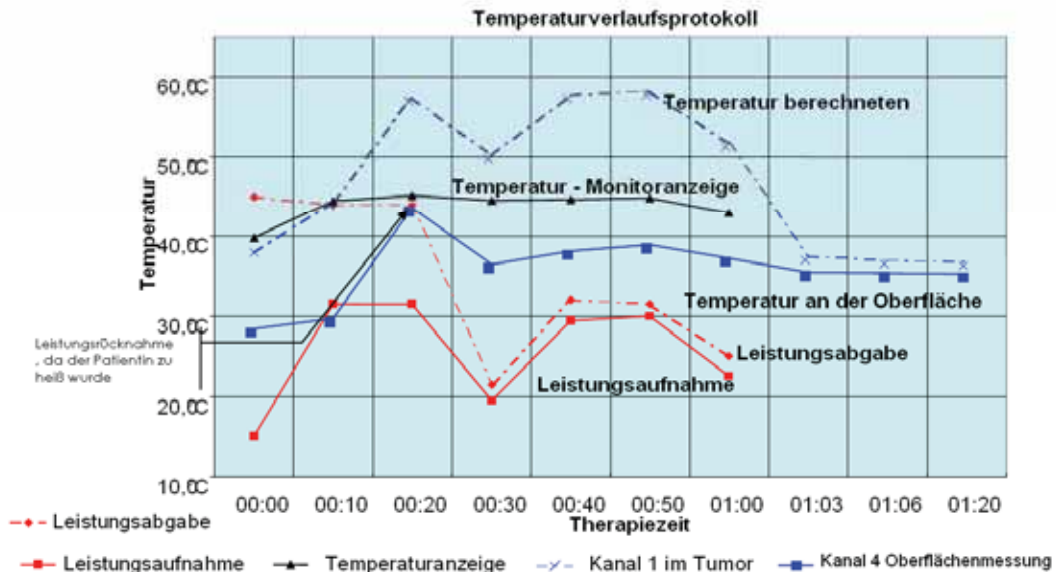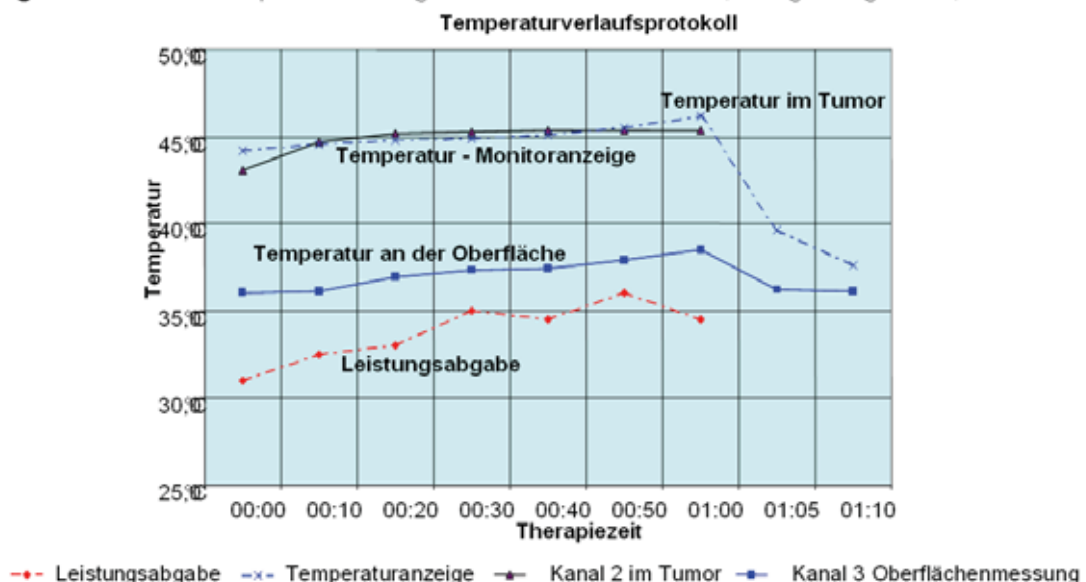
Anmerkung: Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.

Thermo-control (invasive)

St. Georg Klinik, Bad Aibling, 2001

Patient:
Diagnose: Cervix-Ca.
Therapiekombination: Tiefen-Hyperthermie
Messung vom: 05.01.2001
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C

Temperaturverlaufsprotokoll

−◆− Leistungsabgabe   −×− Temperaturanzeige   −▲− Kanal 2 im Tumor   −■− Kanal 3 Oberflächenmessung

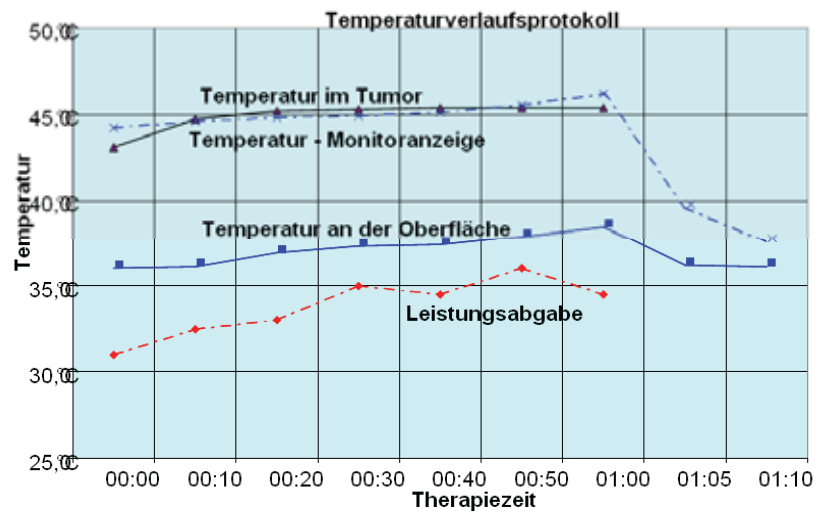**Anmerkung:** Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.

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Invasive Temperaturmessung

Diagnose: Cervix-Ca.
Therapiekombination: Tiefen-Hyperthermie
Messung vom: 05.01.2001
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C
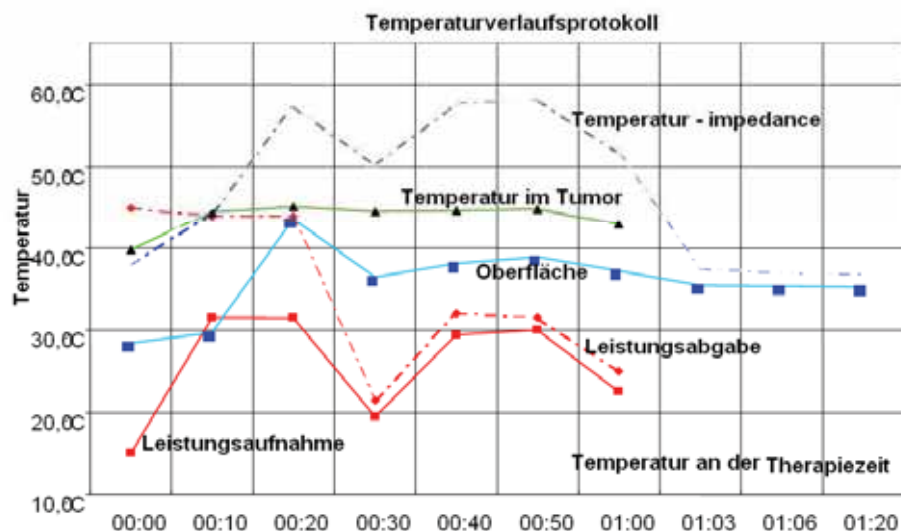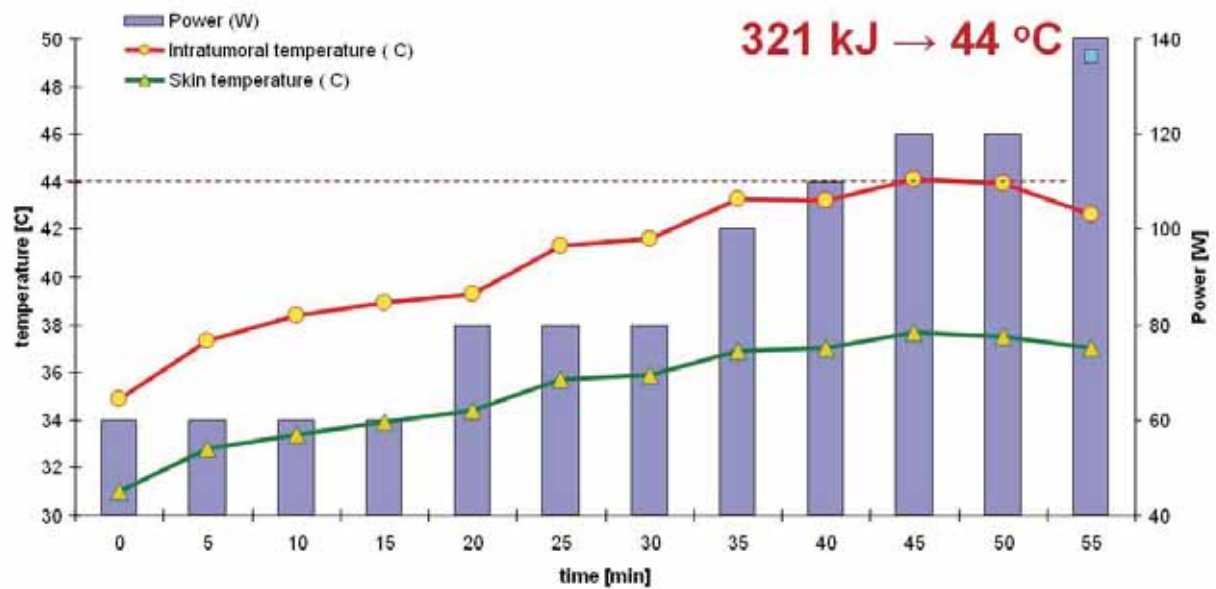
St. Georg Klinik, Bad Aibling, 2001

Temperaturverlaufsprotokoll

- —♦— Leistungsabgabe
- —▲— Temperaturanzeige
- —×— Kanal 2 im Tumor
- —■— Kanal 3 Oberflächenmessung

Anmerkung: Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.

Thermo-control (invasive)

St. Georg Klinik, Bad Aibling, 2001

Patientin: K., geb. 29.12.1940
Therapiekombination: Oberflächen-Hyperthermie und Chemotherapie (Cisplatin)
Messung vom: 04.01.2001
Therapiegerät: Hyperthermiesystem EHY 2000 der Onco-Therm GmbH
Messeinrichtung: Invasive Temperaturmessung der Fa. Onco-Therm GmbH; Messgenauigkeit < 0,1 °C

Temperaturverlaufsprotokoll

- —♦— Leistungsabgabe
- —■— Leistungsaufnahme
- —▲— Temperaturanzeige
- —■— Kanal 4 Oberflächenmessung

Anmerkung: Die Leistungsabgabe und die Leistungsaufnahme wurden in Watt gemessen und für die graphische Darstellung jeweils durch 2 dividiert.
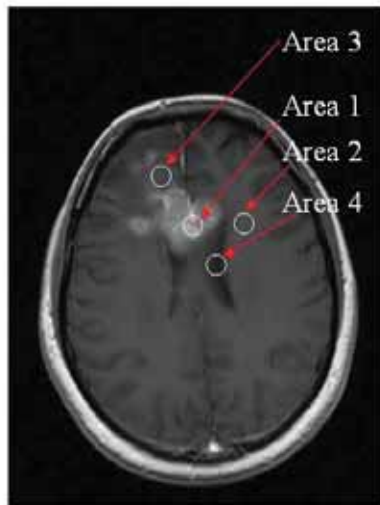
81

Oncothermia Mammary CA

Investigator: Prof.D.Gronemeyer & Dr.H.Sahinbas (2002)
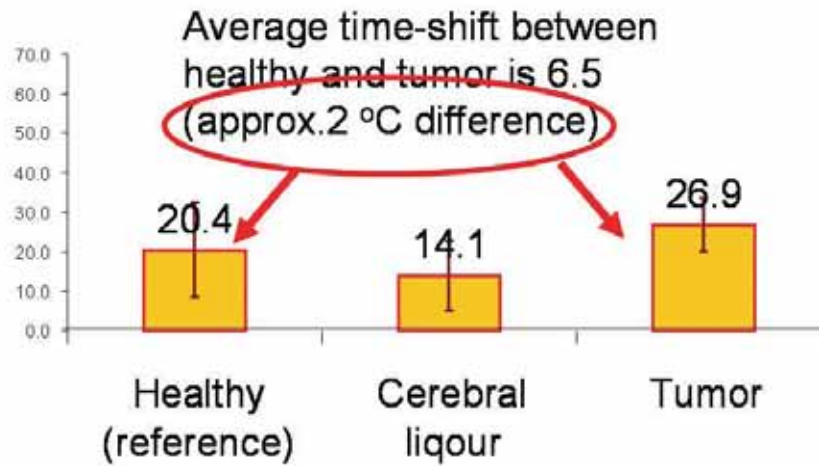**Department:** Department of Radiology and Microtherapy, University of Witten-Herdecke, Bochum, Germany

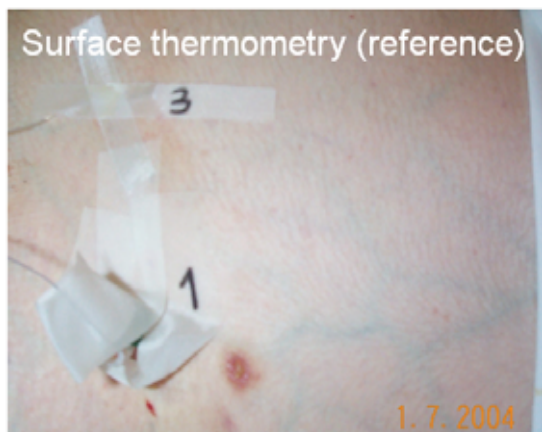# EXPERIMENTAL SETUP: WITH OPEN MRI TOSHIBA 0.062T

Area 3
Area 1
Area 2
Area 4

Average time-shift between healthy and tumor is 6.5 (approx. 2 °C difference)

20.4   14.1   26.9

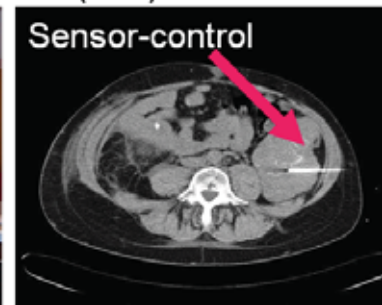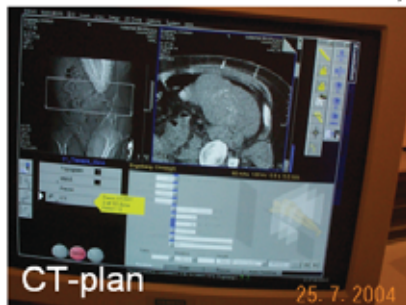Healthy (reference)   Cerebral liqour   Tumor

Prof. Gonemeyer & Dr. Sahinbas Husein,
Univ. Witten Herdecke, (2004)

CT guided invasive thermometry

Abdomen measurement, 12 cm depth, Bochum, Dr. H.Sahinbas (2004)

CT-plan   25. 7. 2004   CT arrangement   25. 7. 2004   Sensor-control

Surface thermometry (reference)   1. 7. 2004   Tumor-thermometry   1. 7. 2004
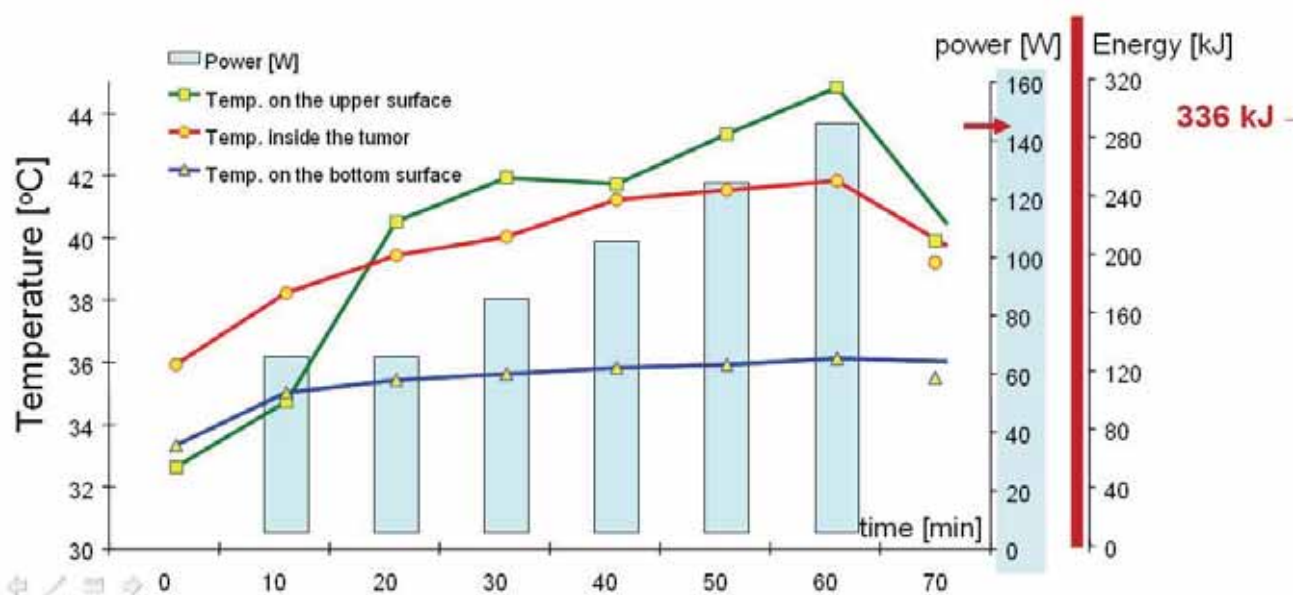
Investigator: Prof.D.Gronemeyer & Dr.H.Sahinbas (2005)
Department: Department of Radiology and Microtherapy, University of Witten-Herdecke, Bochum, Germany

Invasive thermometry

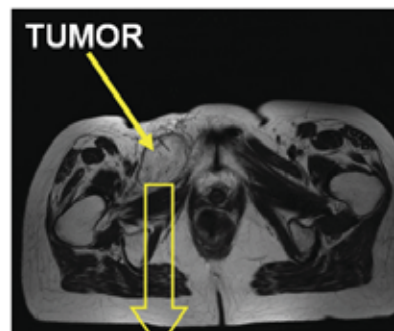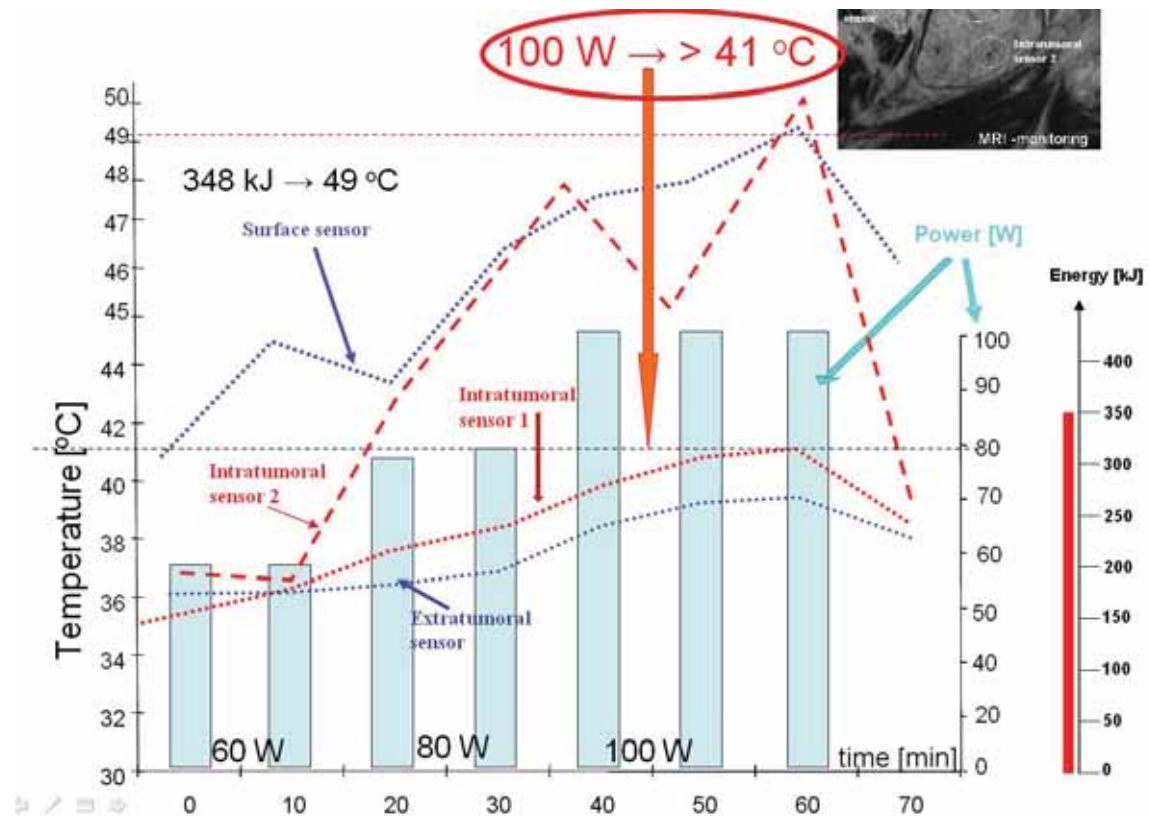## Temperature measurement, Soft-tissue-Sarcoma

Investigator: Prof. Dr. H. Renner
Institution: Klinikum Nord, Nurnberg, Germany
Patient: FP, male, 87y;
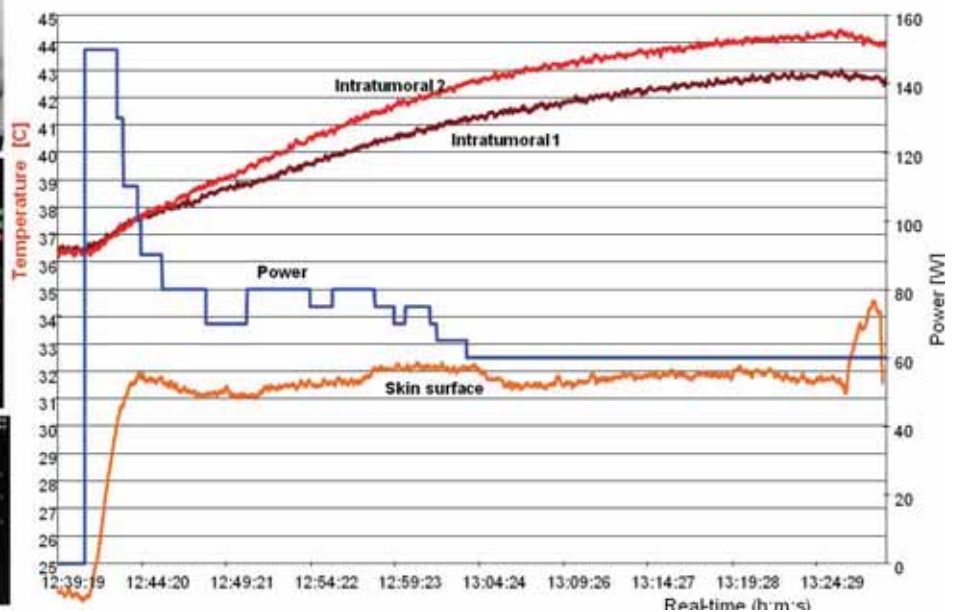**Tumor:** Soft-tissue sarcoma on the right side of the back,
Primer diagnosis: 12/07 CT-guided biopsy
Histology: Malignant fibrotic hystiocytoma G3
Therapy: curative, Radio-Thermo-Therapy (Double-modality)

Intratumoral in situ temperatrure measurement first
Oncothermia, afterwards radiotherapy, Dosis 22 Gy, 6 Fractions

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