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Current Status of Clinical HYPERTHERMIA



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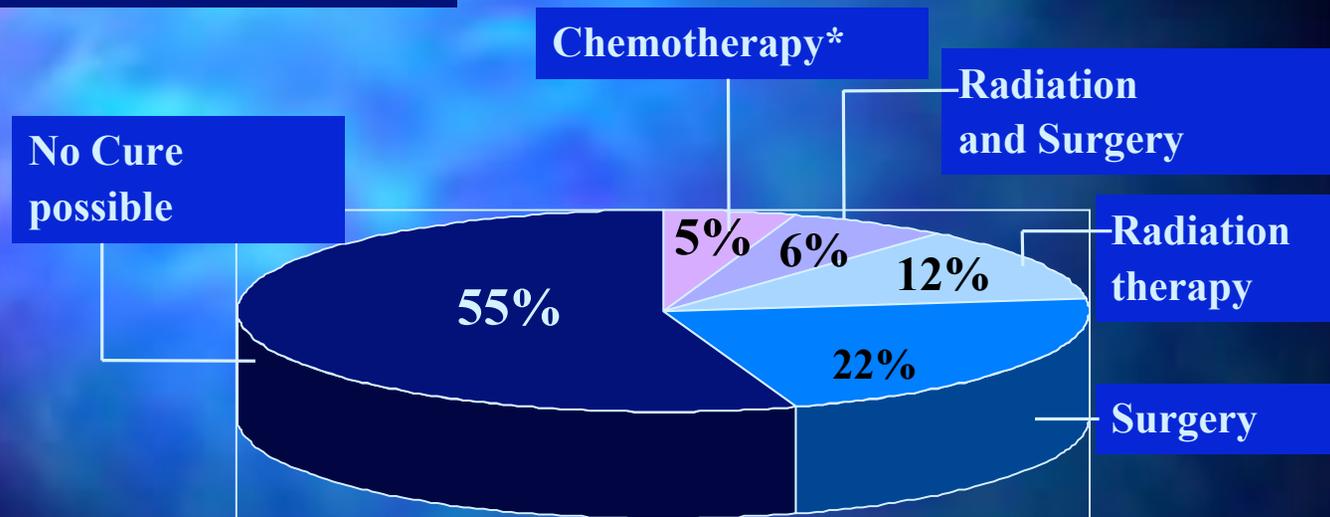


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Previous therapies and outcome

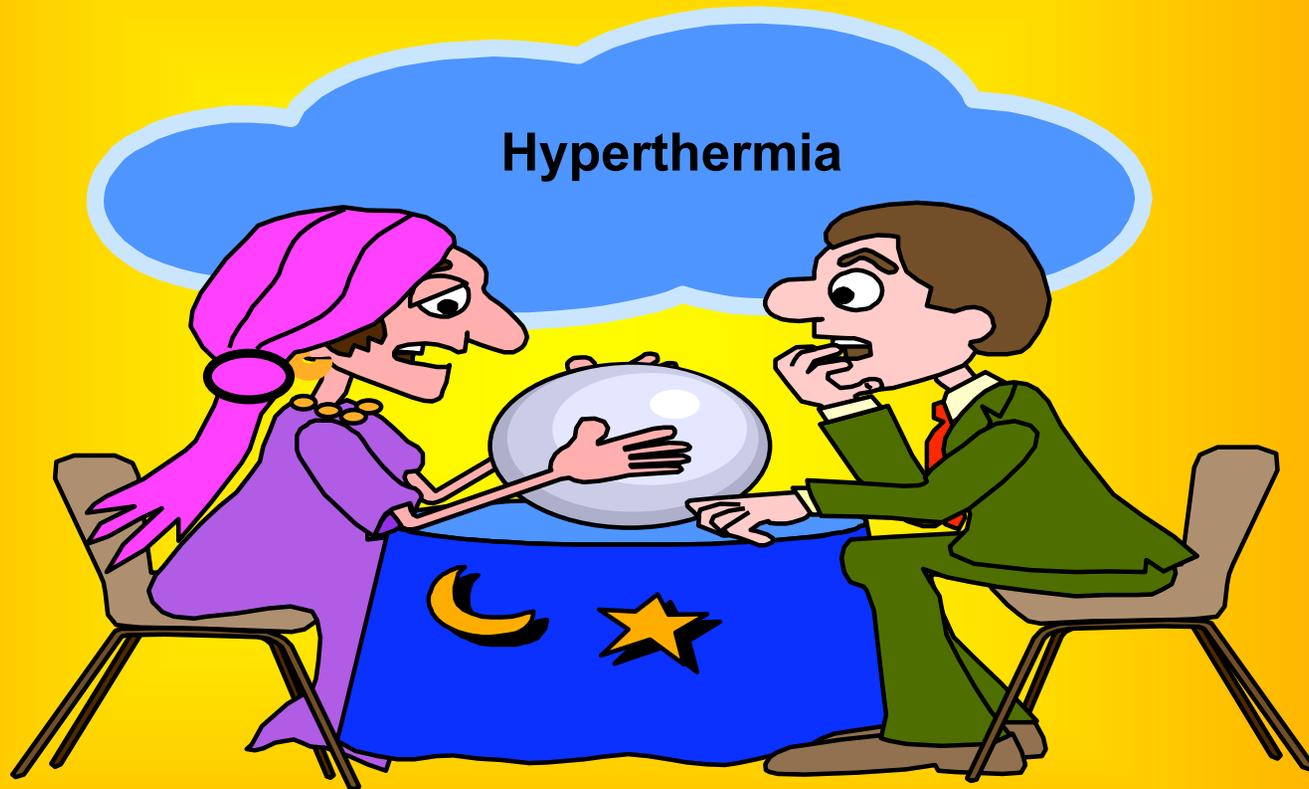
5-J.- Survival



DeVita : Progress in Cancer Therapy , 83

* in Combination with radiation

HYPERTHERMIA



What can I see? Uhuh!

Overview of hyperthermia methods:

I. Active hyperthermia (fever, medical drugs)

II. Passive hyperthermia (device)

A. Whole Body Hyperthermia (WBH)

Mild ($39-40$ °C)

Moderate (40-41 °C)

Extreme ($>42,8$ °C)

B. „Local“ Hyperthermia“

Invasive:

RF, LITT, ECT,

Intracavitary,

Peritoneal,..

Non Invasive:

Local (surface)

Regional (deep)

Locoregional (=EHT)

Locoregional Radiowave Electrohyperthermia (EHT)



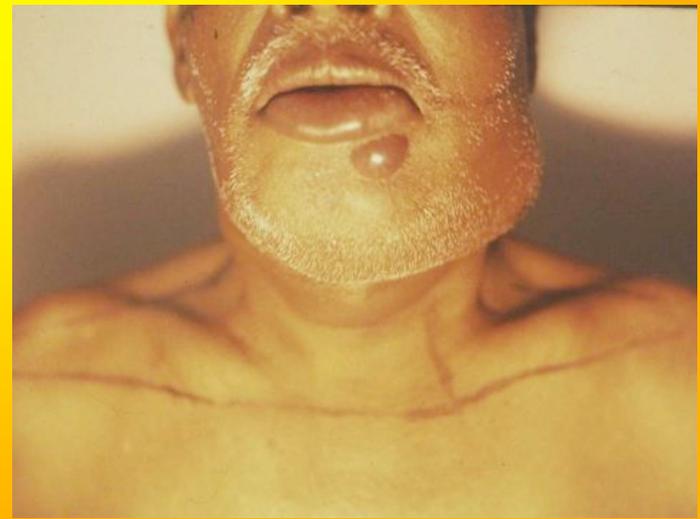
Electromagnetic energy transfer with 13.56 MHz, low-frequency modulation, selective targeting of extracellular fluid of the malignant cells with heat accumulation and over-heating.

Typical applications of EHT

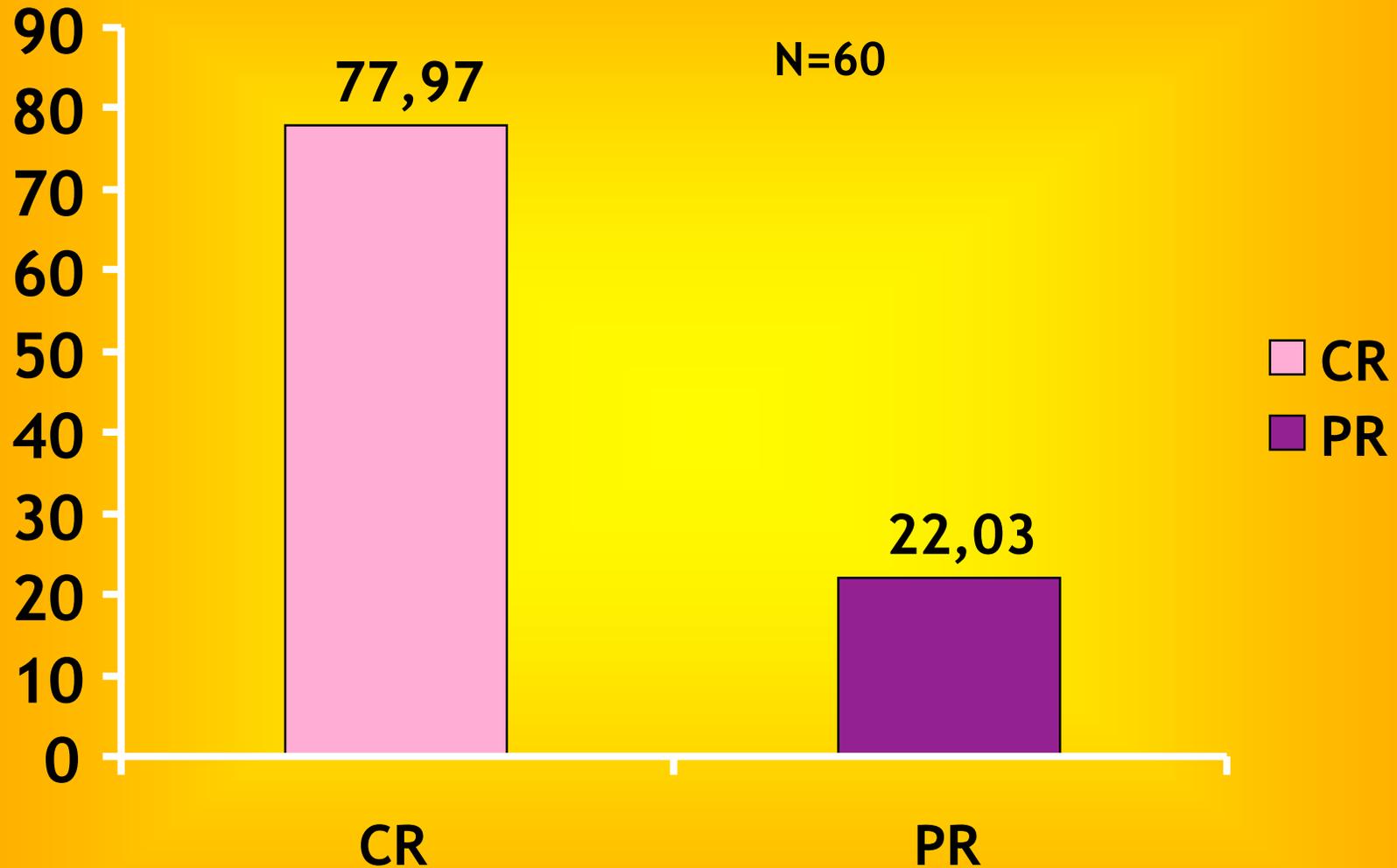
- **Solid tumors:** tumour destructive technique without side-effects, during which the treatment of tumours takes place in several sessions
- **Metastasis:** regional treatment of largest tumour region; several treatments by different regions is possible direct after another.

Selected Tumor Entities Treated with Regional Hyperthermia

Hyperthermia in Head & Neck



Initial Response Following HT + RT



Hyperthermia in Head & Neck

Phase-III-Study (Valdagni and Amichelli in Italy):

Non resectable head-neck-cancer grade IV with metastases in lymphnodes.

Radiotherapy (RT) + Local Hyperthermia (HT)

n= 41 patients

RESULTS:

CR (complete remission):

RT: 41%

RT + HT: 83%

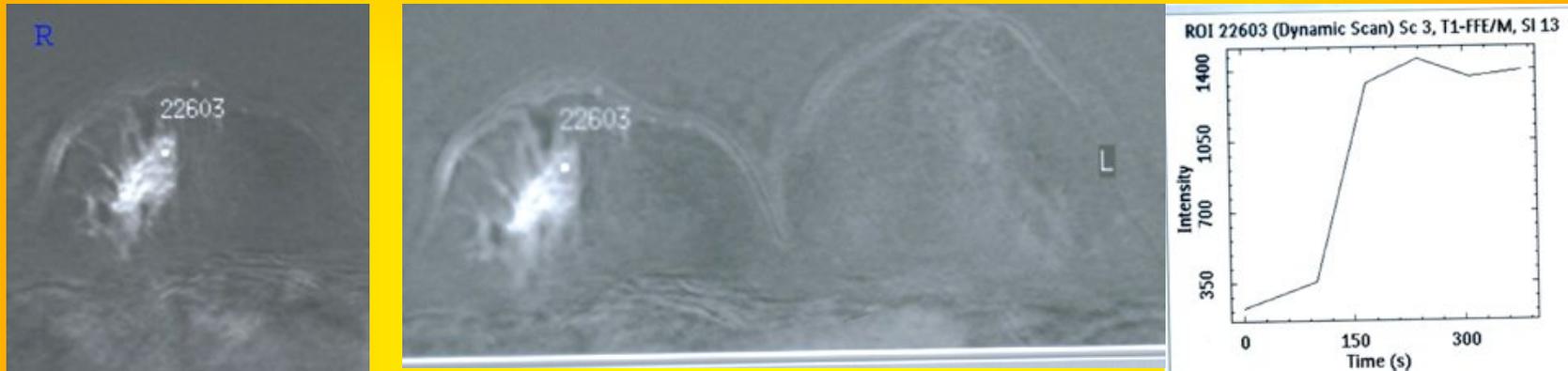
5-Years-Survival:

RT: 0%

RT + HT: 53%

Hyperthermia in Breast Cancer

Before HT and Chemotherapy 17.10.02



After HT and Chemotherapy 06.03.03



Since 17.10.02 to
05.02.03

3x

Taxotere + Epirubizin
every 3 weeks

Hyperthermia in Breast Cancer

ESHO 2007:

109 Patients with relapsed **MAMMA Ca**

THERAPY:

- Radiationtherapy + Hyperthermia
- Radiationtherapy alone

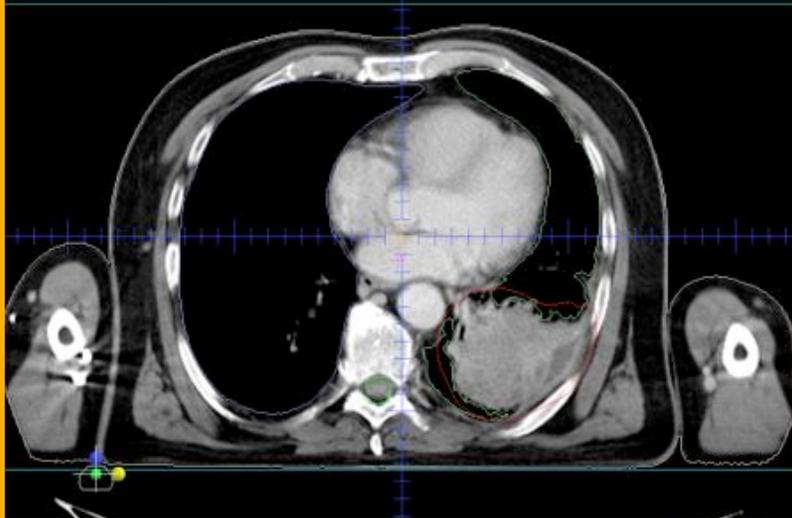
RESULTS:

→ Hyperthermia-group CR: 68%

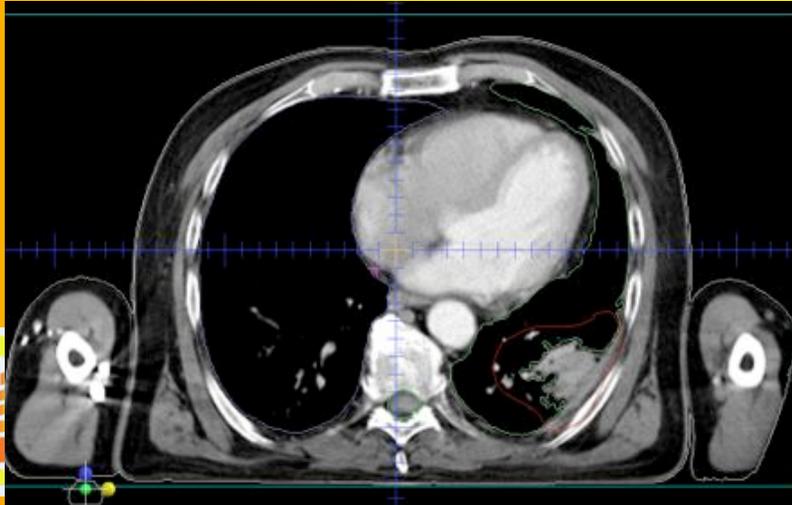
→ Non hyp.-group CR: 24%

Hyperthermia in Lung Cancer

Before therapy



after therapy 50 Gy + Hyp



Patient G.A., 68 years, m.

BC left ul

cT3 cN2 M0 G3 R2

Histology: Plattenepithel-Carzinom

Therapy:

60 Gy,

Cisplatin 1x/Week 5x, 10 HT

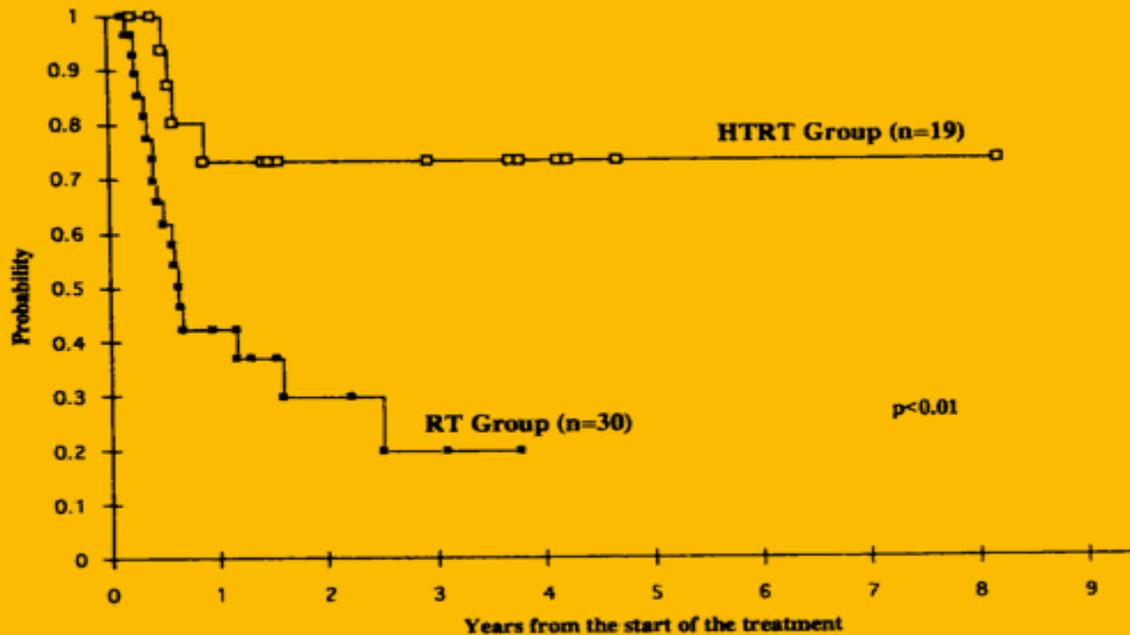
8 Weeks post RT-CT-HT,

Lung-resektion R0,

Histology: No Tumor cells

Hyperthermia in Lung Cancer

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: RT vs. RT+HT



Result:

HT+RT: 74% after 7 J.

RT: 21% under 4 J.

diffus metast. Pancreatic cancer G3

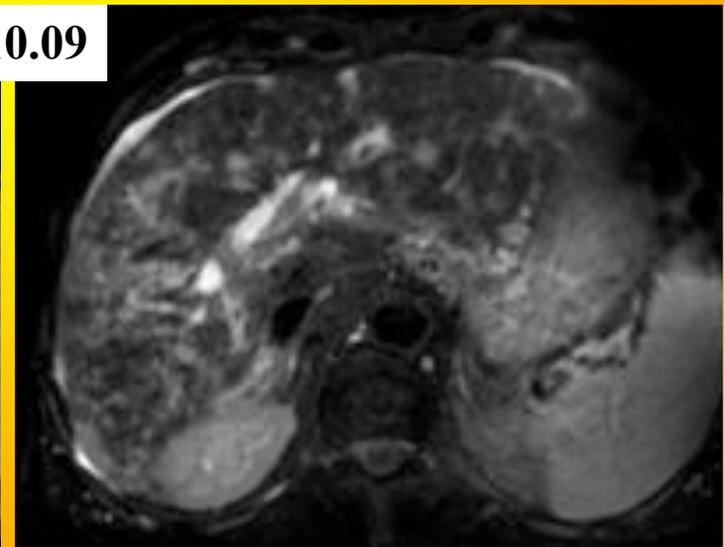
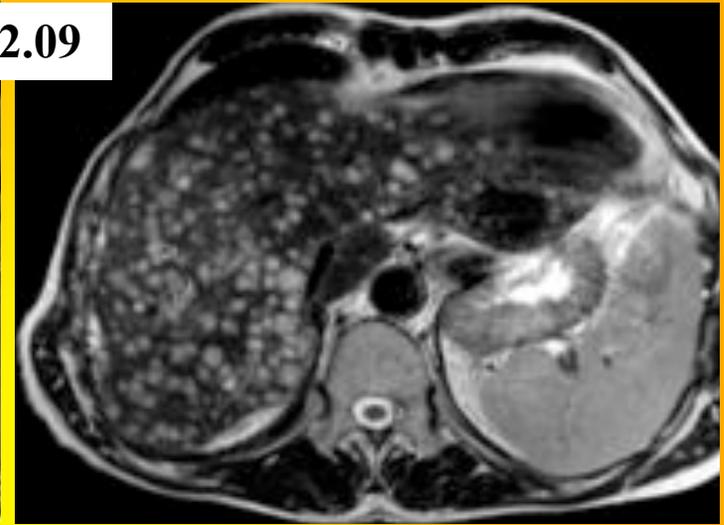
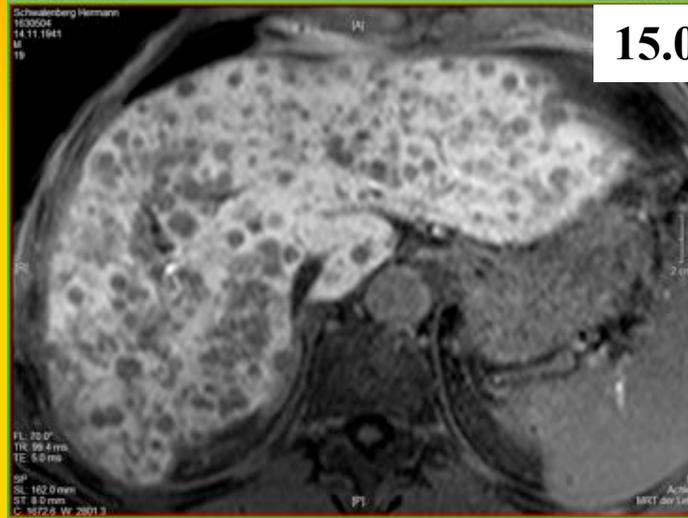
neoadjuvant Therapy,
SIRT-Therapy 07-08.08,
Radiotherapy abd. LK
06.02. – 17.03.2009 PD;
since 02.09 ongoing
Chemotherapy,

Since 02.2008 Fatigue +
tumoranämia

MRI:04.09 → PD

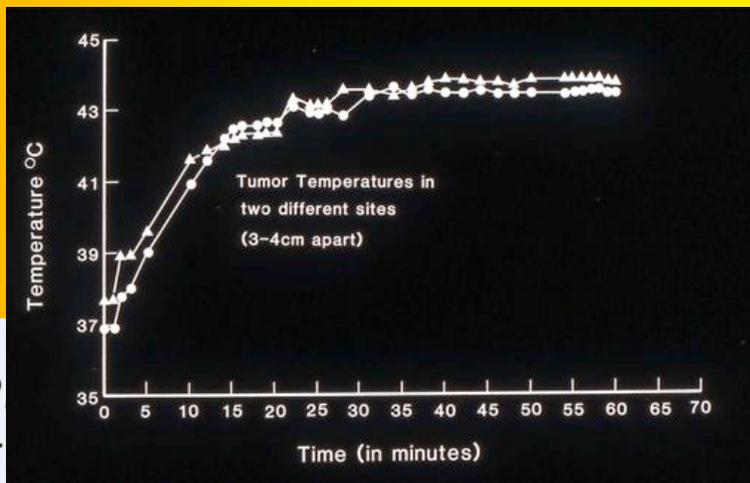
CxT + **hyperthermia**

MRI: 10.09 → PR



Hyperthermia in Pancreatic Cancer

Temperature monitoring



Hyperthermia in Pancreatic Cancer

3 explorative trials presented at ICHO 2008: Verona, Munich and Kyoto

<u>Takagi et al, Kyoto:</u>	for Gemcitabine plus HT	versus	for Gemcitabine alone
	57 % disease control (CR+PR+SD)	„	14 %
	49 % 1 year OS	„	30 % (p=0,024)

<u>Maluto et al , Verona:</u>	for Chemo + Radiation plus HT	versus	for Chemo /Radiation alone
	68 % 1 year OS	„	47 %

no more toxicity observed as in control group

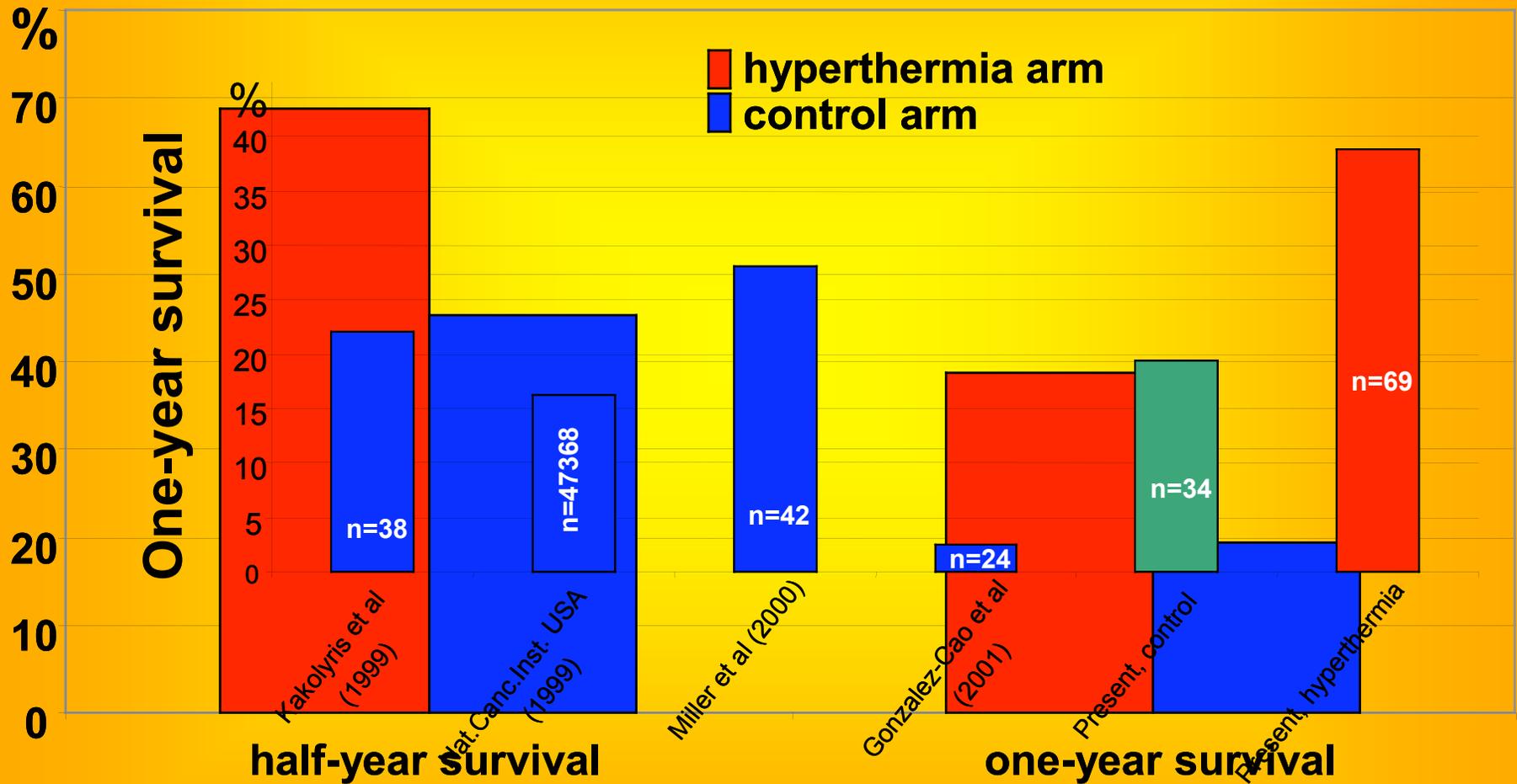
Tschoep et al, Munich: for Gemcitabine/CIS plus HT as second line therapy!

median progression free survival from start 2 nd line therapy:	4,2 months (CI: 2.1-7.7)
median OS:	16,9 months (CI: 11,8-22)

all presented at: *ICHO conference, 10th International Congress on Hyperthermic Oncology, Munich, Germany 2008*

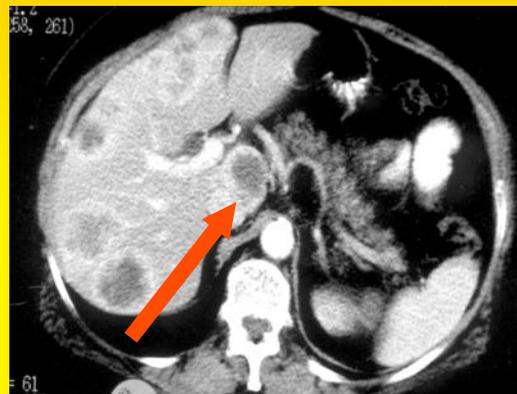
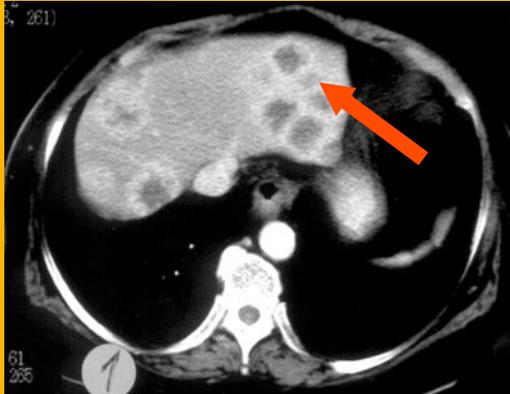
Pancreatic Cancer

Retrospective Study n=69

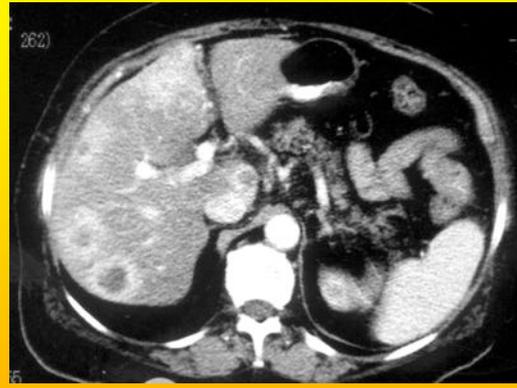
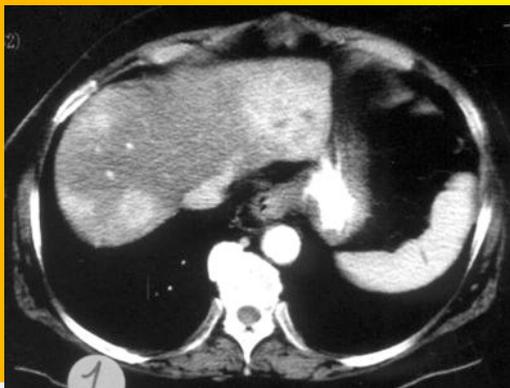


Metastatic Colon Cancer

Before HT 03.07.01 with XELODA



During Hyperthermia 22.11.01 + XELODA



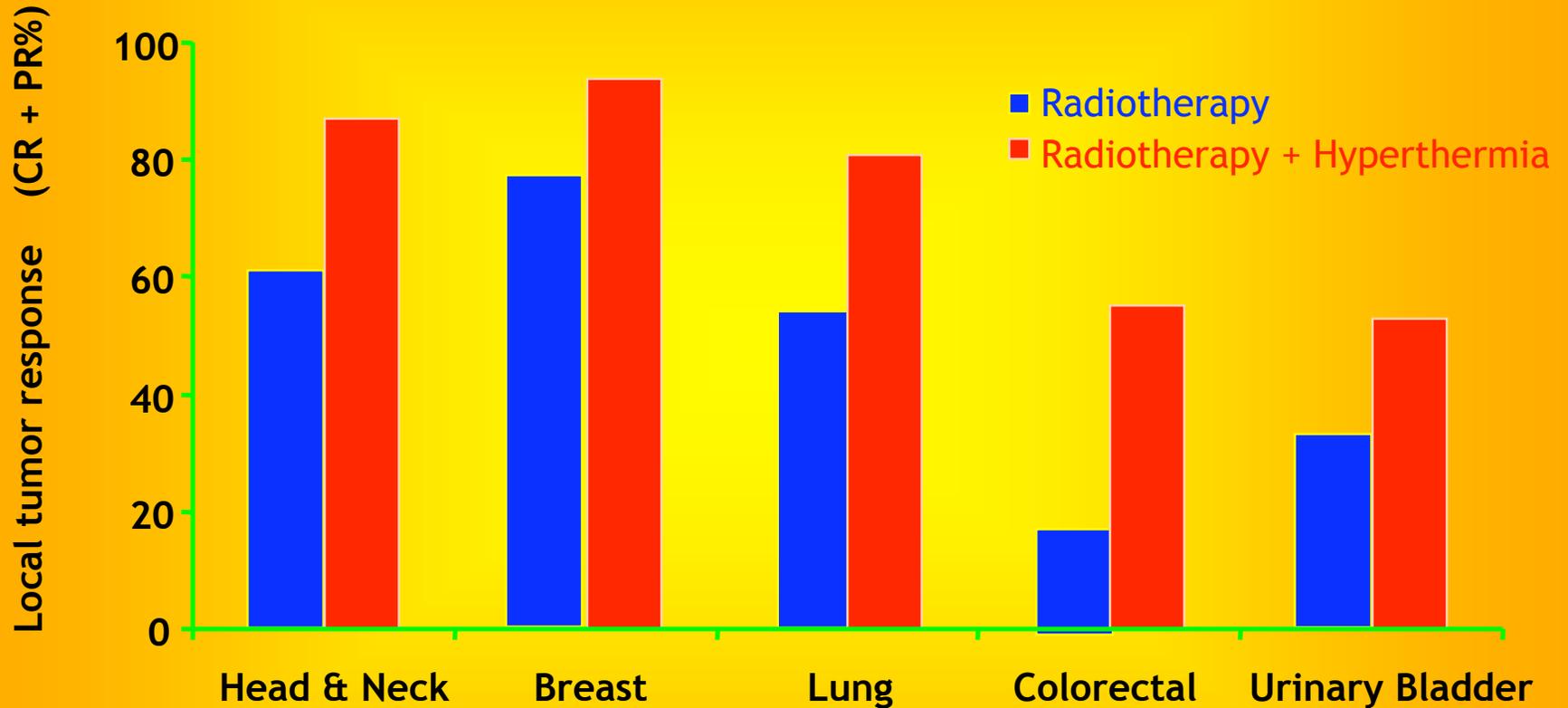
Metastatic Colon Cancer + HT n=80

Treatment method	1 year survival	3 years survival
Chemotherapy	48 - 58 %	14 - 19 %
HT + Chemotherapy	91 ± 3 %	31 ± 6 %

D.Hager et.al.: Anticancer Res. 19, 3403-08, 1999

Randomised controlled trials with HT

Statistics based on 44 clinical articles, including 1963 cases



The tumor response according to various tumor sites by the combination treatment with hyperthermia and radiotherapy.

Randomised controlled trials with HT

Tumor site	Experi- mental	Con- trol	No. of Pts.	OR [%] Control	OR [%] with HT	Ref.
Cervix	RT + HT	RT	65	46	66	57
Cervix	RT + HT	RT	66	35	72	58
Cervix	RT + HT	RT	37	53	83	59
Cervix	RT + HT	RT	40	50	85	60
Colorectal	RT + HT	RT	24	10	43	26
Gastric	RT + HT	RT	293	35,5	57,6	33
Colorectal	RT + HT	HT	71	36	54	61
Bladder	RT + HT	HT	49	48	83	62

[26] Hiraoka M, et al: Clinical results of radiofrequency HTcombined with RT in the treatment of radioresistant cancers. Cancer 1984, 54:2898-2904

[33] Shchepotin IB et al.: Intensive pre operative RT with local HT for the treatment of gastric carcinoma. Surg Oncol. 1994 Feb;3(1):37-44

[57] Datta NR, Bose AK, Kapoor HK: Thermoradiotherapy in cervix (IIIB): a controlled clinical study. Indian Med. Gazette 1987; 121:68-71

[58] Hornbach NB, et al: Advanced stage IIIB cancer of the cervix treatment by hyperthermia and radiation. Gynecol. Oncol. 1986- 23:160-167

[59] Harima Y, et al: randomized clinical trial of RT+HT versus RT in stage IIIB cervical carcinoma. Int J Hyperthermia 2001 Mar; 17(2):97-105

[60] Harima Y., et al. A randomized clinical trial of RT versus RT+HT in stage IIb cervical carcinoma. Int J Hyperthermia 2001; 17:97-105

[61] Nishimura Y, et al (1992) HT +HT for primary unresectable and recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 23:759-768

Deep Electro-Hyperthermia in **relapsed malignant gliomas** treated with Radiofrequency Hyperthermia at 13.56 MHz

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Department of Radiology
Dr. H. Sahinbas
ASCO 2008

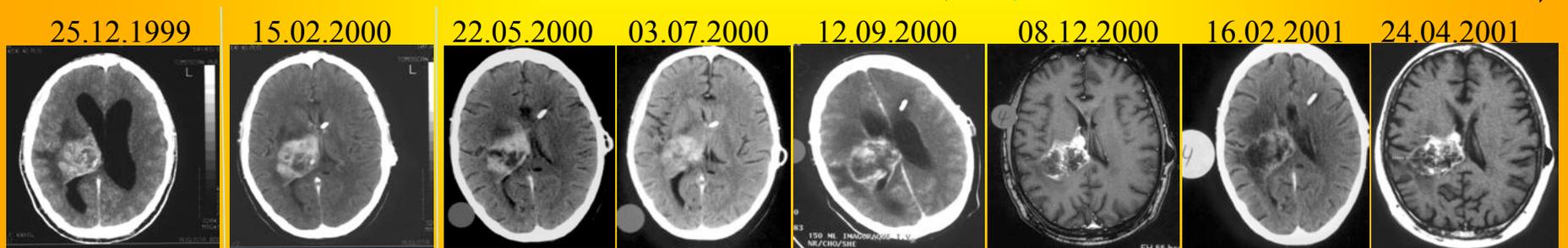
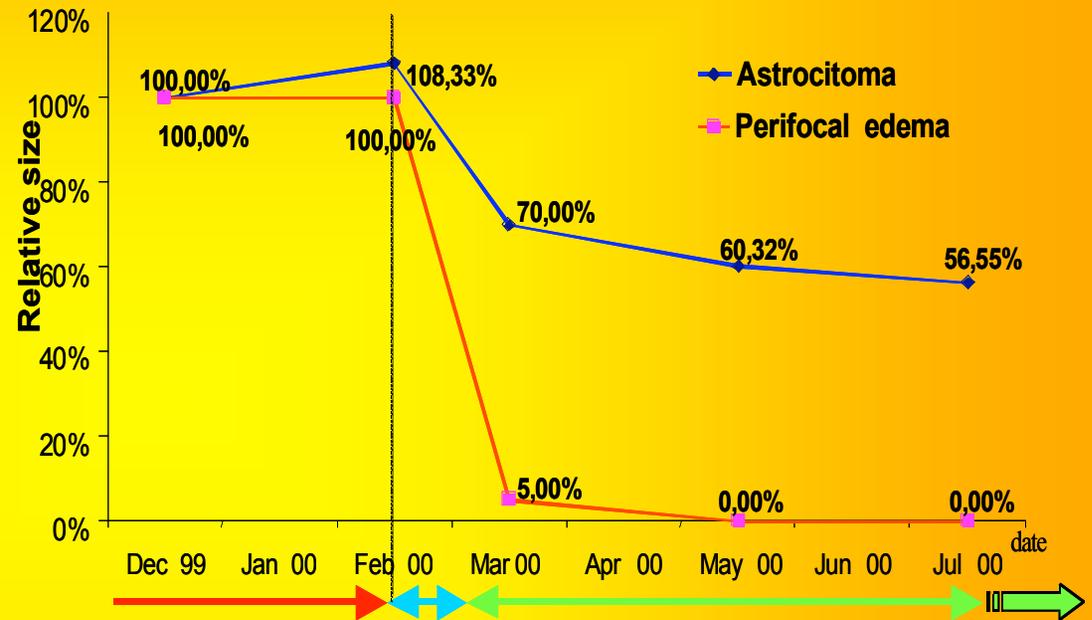
Treatment combination (example)



ASTROCYTOMA WHO III TREATMENT WITH ELECTRO **HYPERTHERMIA (EHT)**

University Witten-Herdecke, Gronemayer Institute of Microtherapy, Bochum, Germany , Dr. Sahinbas H.

1st diagn: 12/99 Astrocytoma, Hydrocephalus oclusus, neurofibromatosis; WHO III_Non-operable
 Tu: 4 x 5,6 x 3,6 + edema 2 cm compression of Ventrikels, Hydrocephalus oclusus, left side paralyses, disable of concentration, epileptic attacs KI: 30-40 %
Medication: Fortecotin 4 mg (16.02.00 - 28.03.00.)
Radiation: 01/00 bis 02/00 bis 40 Gy + 20 Gy (2 Gy/d)
EHT as MONOTHERAPY:
 16.02.- 28.03.00 16 x EHY, 20.04.- 04.05.00 6 x EHY
 18.06.- 03.07.00 6 x EHY, 11.12.- 16.02.01 14 x EHY
Results:
 shrinking of tumor edema, central tumor necrosis
 shrinking of tumormass, shrinking of neur.sympt.
 KI: 90-100 % since October 2002,
 Follow up till excitus: 20.03.03



Shuntocclusion

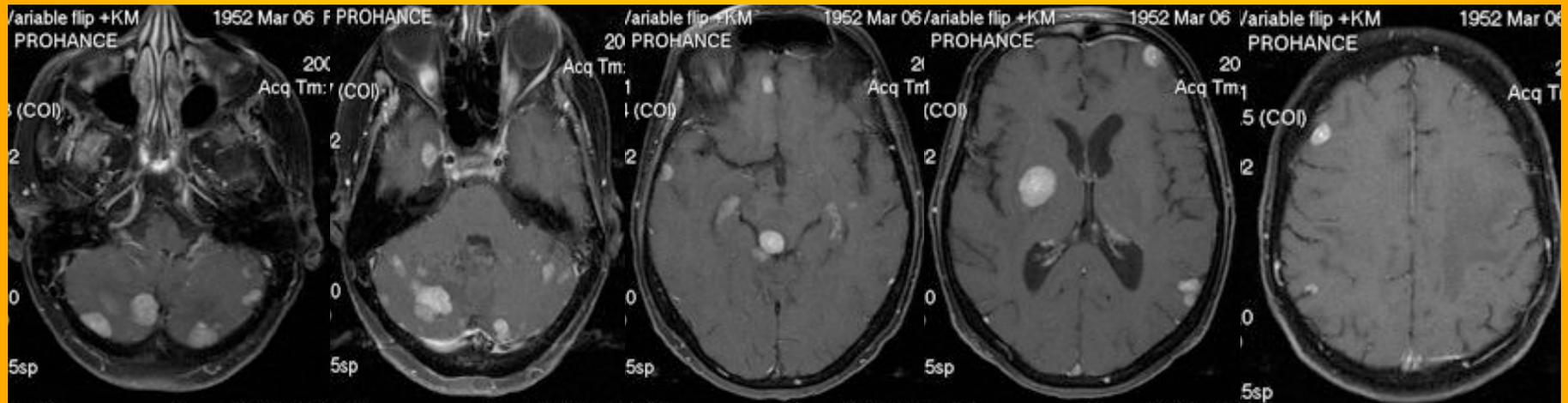
After 4th oncothermia

Before radiation and hyperthermia

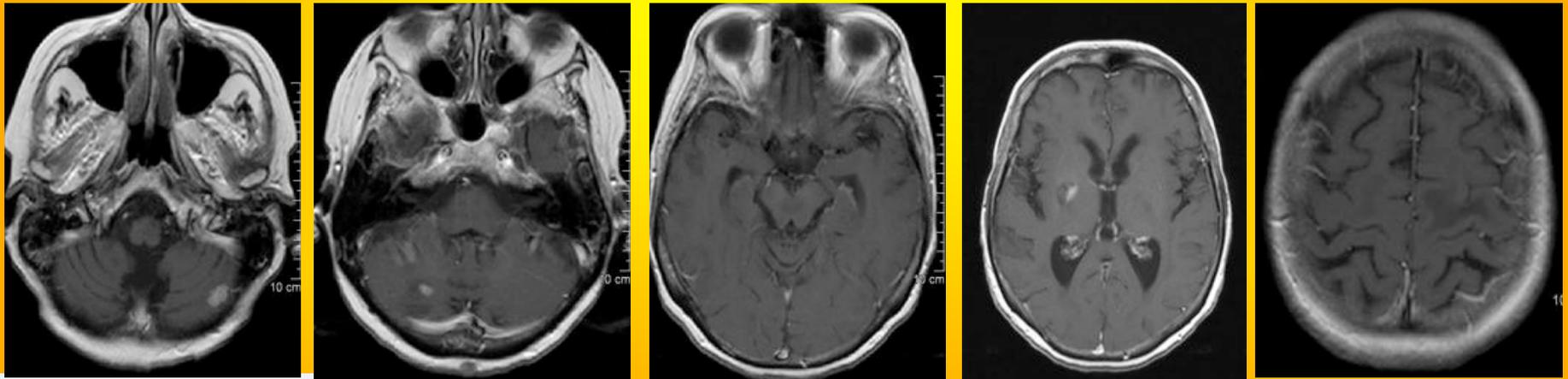
hyperthermia + 6x radiation

hyperthermia + 6x radiation

BRAIN METASTASES FROM BREAST Ca.

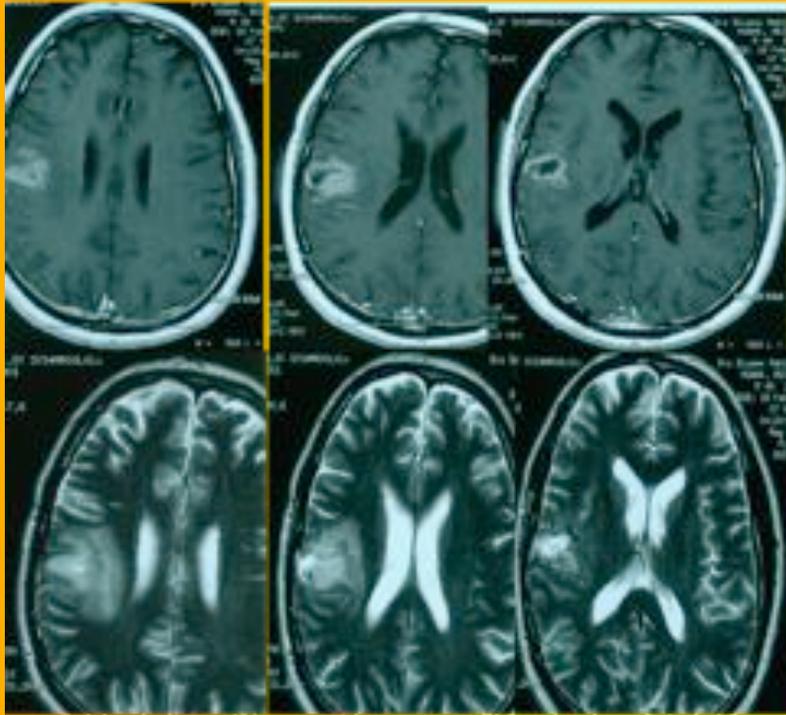


25.01.2006 MRC before Radiation + HT

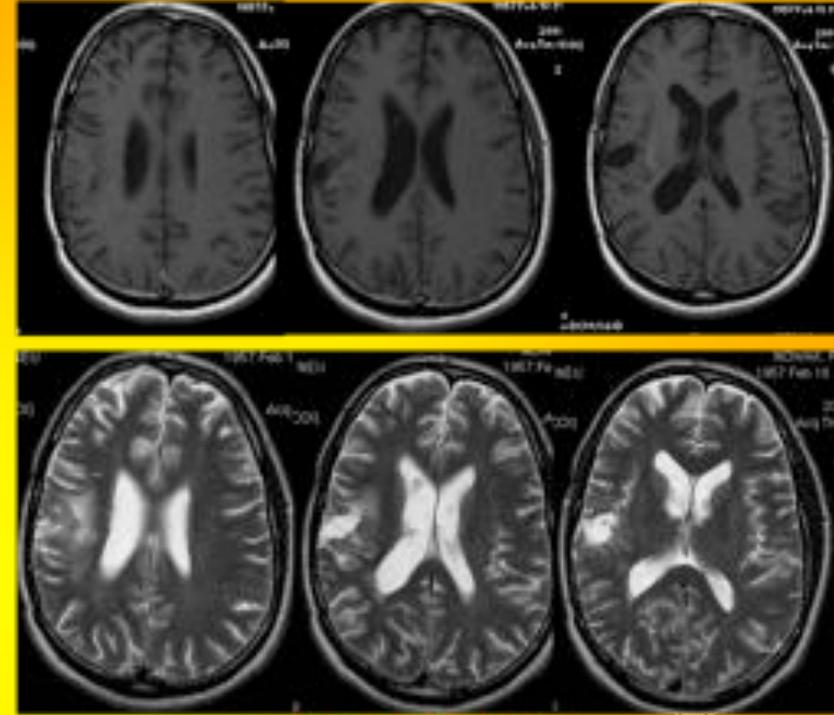


23.08.2007 MRC after Radiation + HT

Glioblastoma multiforme WHO IV



07.11.05 MRI.



10.2009 MRI

50-year-male. **GBM (WHO IV, ED May 2005):** surgery, radiation and chemotherapy.

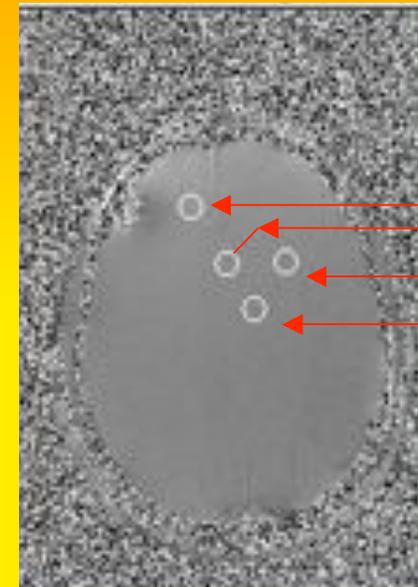
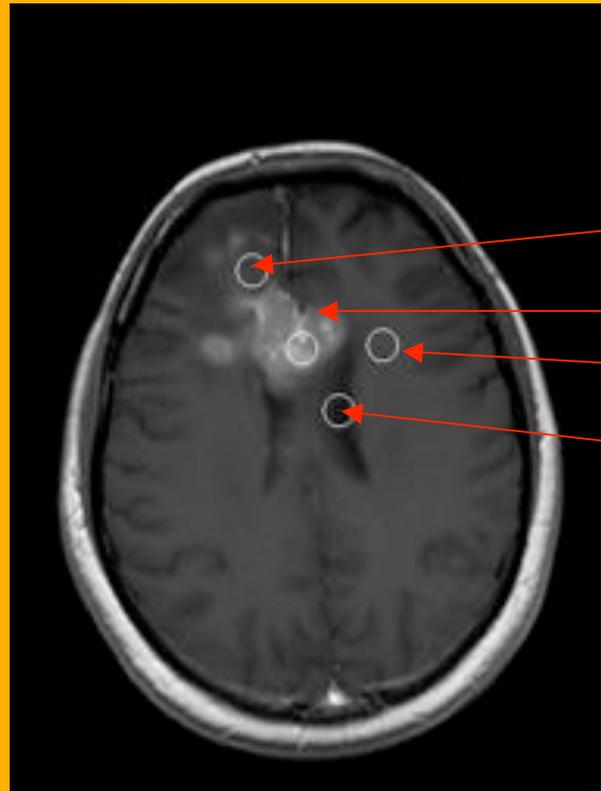
Symptoms: cephalgia, epileptic seizures, aphasia, and motor dysfunction. Laboratory evaluation was without relevant pathologic findings.

Recurrent of GBM WHO IV (10.2005): Surgical intervention was not feasible. → PD

Since February 2006: CxT with temozolomide (100 mg/m²/d x 21 days, one week rest) + RF-HT which is ongoing at the time > 42 month → CR

TEMPERATURE MONITORING BY MRI DURING EHT

Dr.Sahinbas H, Univ.Witten-Herdecke



Area 4

Area 3

Area 1

Area 2

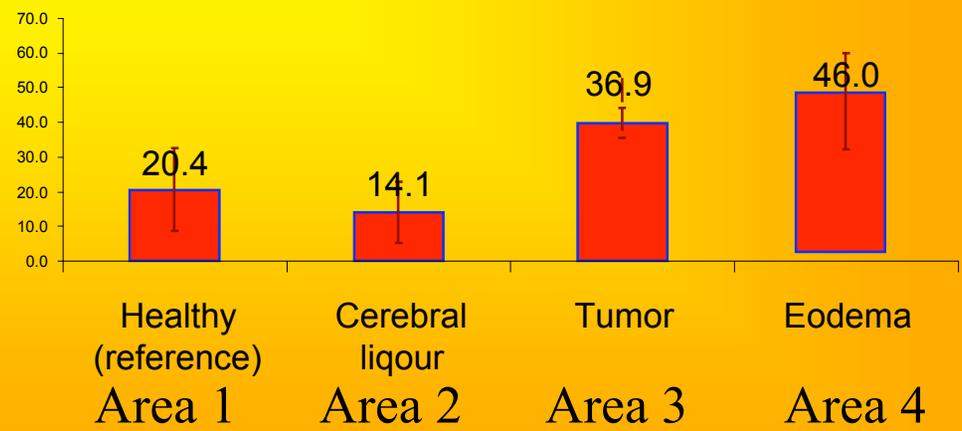
Area 4

Area 3

Area 1

Area 2

mean shift



RESULTS

Hyperthermia may Increase Overall Median Survival Time (MST)

MST of patients with WHO grade III and IV gliomas (Kaplan-Meier-Estimation)		
MST from	Grade III AA; N = 53 pts months ± se [95%CI]	Grade IV GBM; N = 126 pts months ± se [95%CI]
1st Diagnosis of Disease	38.2±3.7 [31.2;45.0]	20.3±1.7 [15.9;22.1]
1st RF-Hyperthermia	10.6±2.0 [6.7;14.4]	7.6±0.9 [5.9;9.3]
Events / Censored N (%)	39 / 14 (26.4%)	101 / 25 (19.8%)

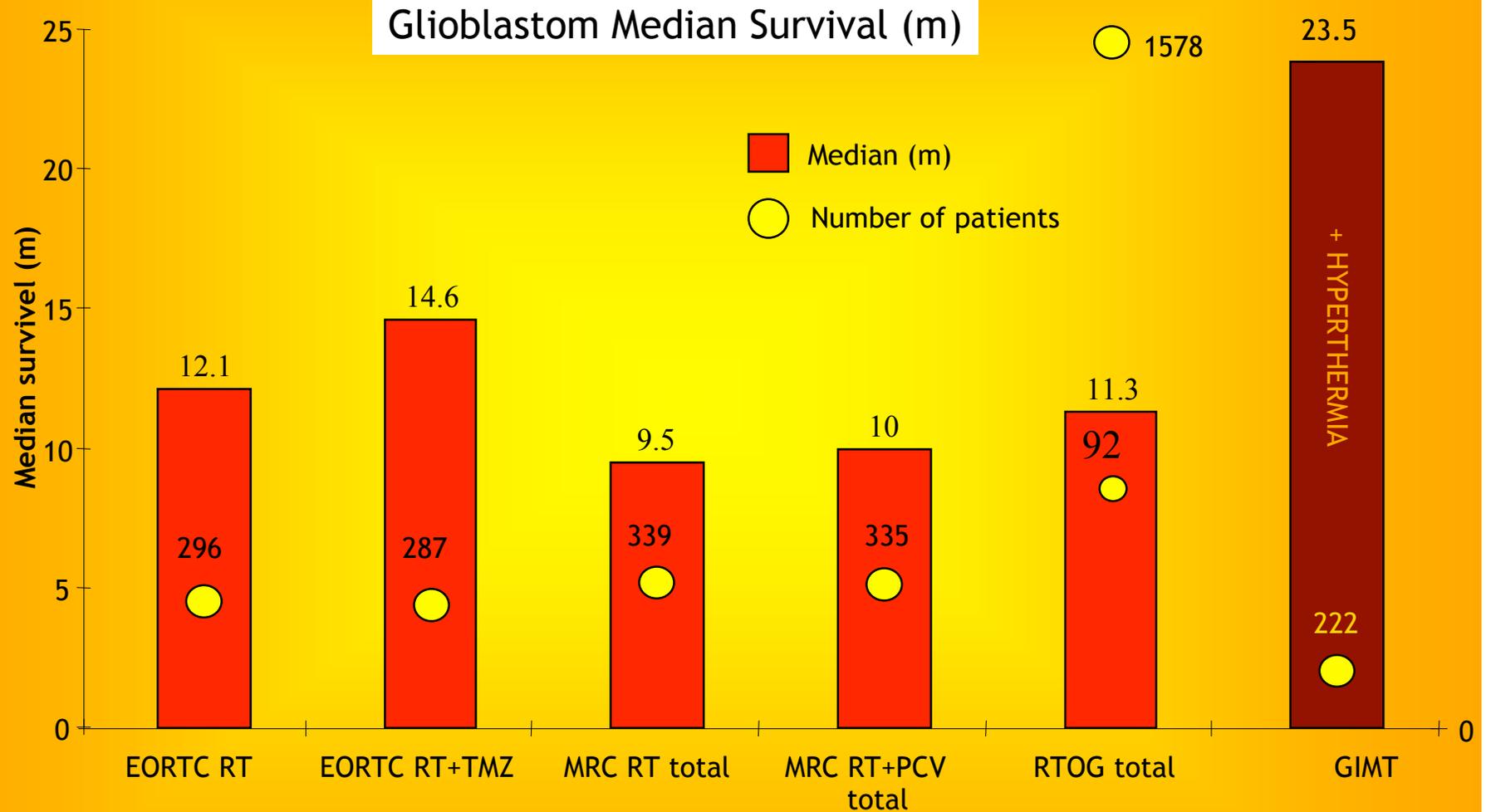
Survival Probability (Kaplan-Meier-Estimation)

From newly diagnosed	1 yr .	2 yrs	3 yrs	4 yrs	5 yrs
AA WHO° III; N=53	96	72	53	35	30
GM WHO° IV; N=126	82	41	23	11	11

Censored (AA): 14 (26.4%); events: 39 (73.6%)

Censored (GM): 25 (19.8%); events: 101 (80.2%)

SURVIVAL TIME IN BRAIN TUMORS



SEER (Surveillance, Epidemiology, and End Results) by the National Cancer Institute USA, April 2000

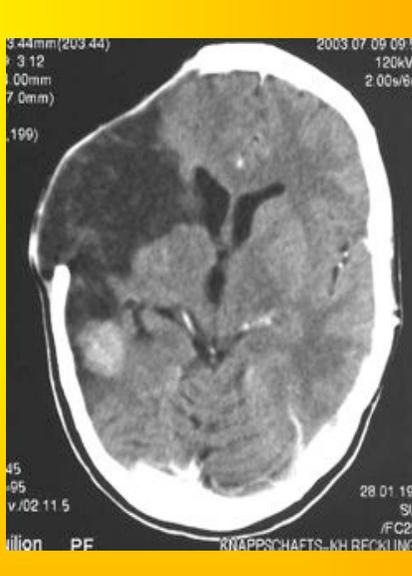
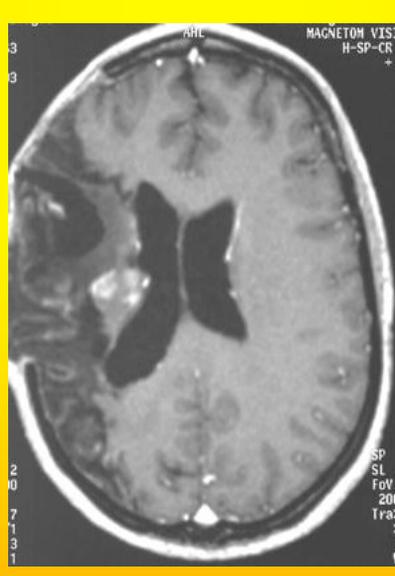
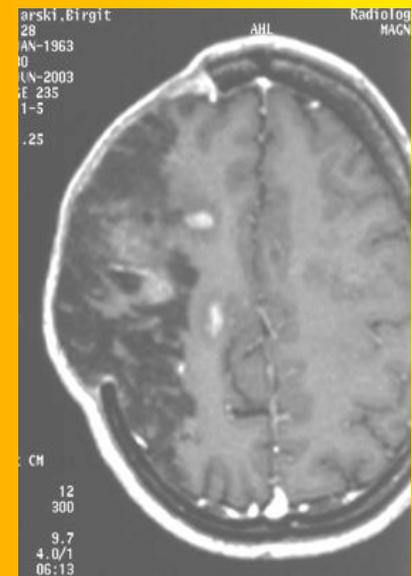
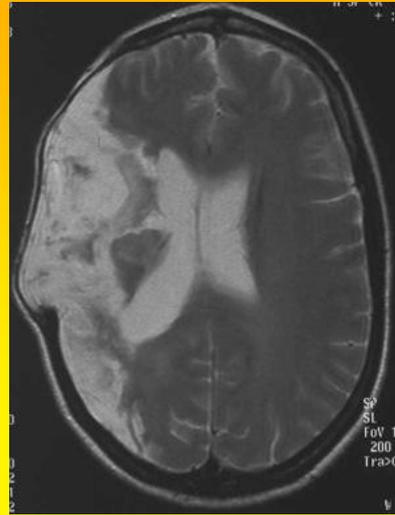
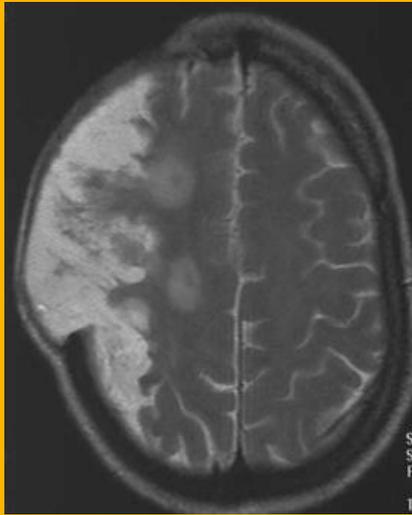
MRC (Medical Research Council, Brain Tumor Working Party)

RTOG (Radiation therapy Oncology Group,

EORTC (European Organisation for Research and Teratment of Cancer)

RT = Radiotherapy, PCV = Procarbazine+CCNU(Lomustine)+Vincristine, TMZ = Temizolomide

Local Hyperthermia ??????



Side effects:

Negative side effects:

A. Short-term (two hours) asthenia after treatment (8-10%)

B. Local redness (rubor) of the skin (8%)

C. Complications: (13%)

- Subcutaneous fibrosis of fat tissue (1%)
- Burning of the skin of one cm in diameter stage I-II (2%)
- After treating brain Tumor: headache and vomiting (12%)

Side Effects:



* The patient was paraplegic and did not feel the burn, thus did not push the pause button.

INTERACTION BETWEEN CHEMOTHERAPY AND HYPERTHERMIA

CISPLATIN (CDDP): FIBROSARCOMCELLS IN COMBINATION WITH CDDP, RT, HT

THERAPY GROUP	EFFECT (DAYS)
CDDP (5mg/kg)	4.4 +/- 0.9
CDDP (10 mg/kg)	8.0 +/- 1.7
34 °C, 30 min.	1.4 +/- 0.7
CDDP and HT	5.9 +/- 1.1
Radiatio (5 X 3 Gy)	6.3 +/- 1.5
HT and Radiation	8.4 +/- 2.2
CDDP and Radiation	11.7 +/- 1.8
Radiation > CDDP > HT	13.9 +/- 2.3
CDDP > Radiation > HT	19.3 +/- 3.4
CDDP > HT > Radiation	25.2 +/- 2.8

Source: Towle, L.R., Hyperthermia and drug resistance; Hyperthermia and Oncology, Vol.4 Chemopotiation by Hyperthermia. 1994; 135 - 160

Conclusions & Summary

1. RF Electro-Hyperthermia has the potential to **increase overall median survival time (MST)** for different tumor entities.
 2. Complete and long-term partial **remissions** or stable diseases could be **better achieved**, occasionally even with HT alone
 3. **Quality of life: increased** in most of the cases
 4. Equivalent temperatures measuring is possible
 2. RF Electro-Hyperthermia for **brain tumors**, show a valid treatment potential and can be safely applied.
 3. **No toxicity** problem did occur.
- ➔ **This oncological treatment can be considered a new beneficial method, adjuvant to conventional therapies**

THANK YOU FOR YOUR ATTENTION

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