ICHS Budapest 2018

Therapy of advanced, therapy resistant Pancreas cancer, with local hyperthermia in combination with chemotherapy

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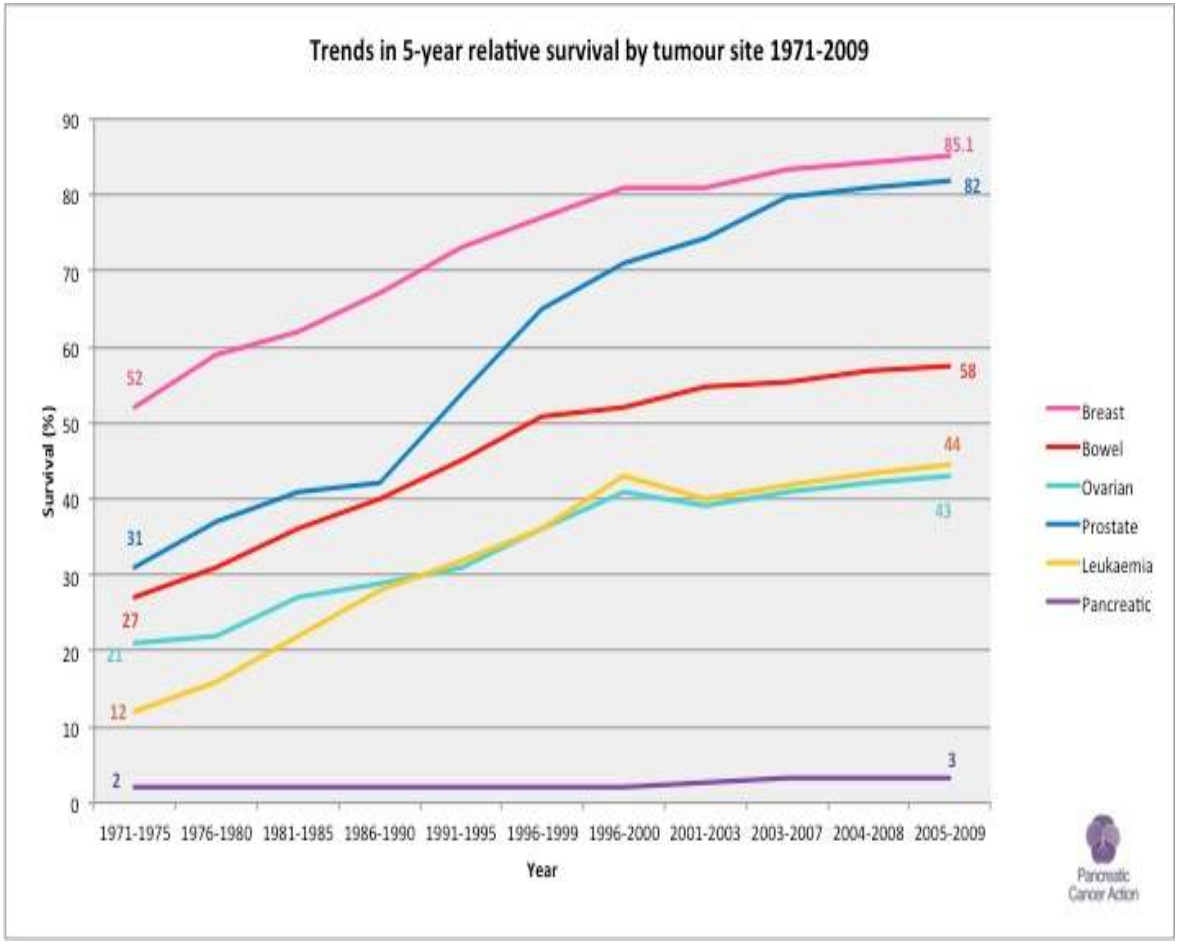
Klinik [illegible] Aibling

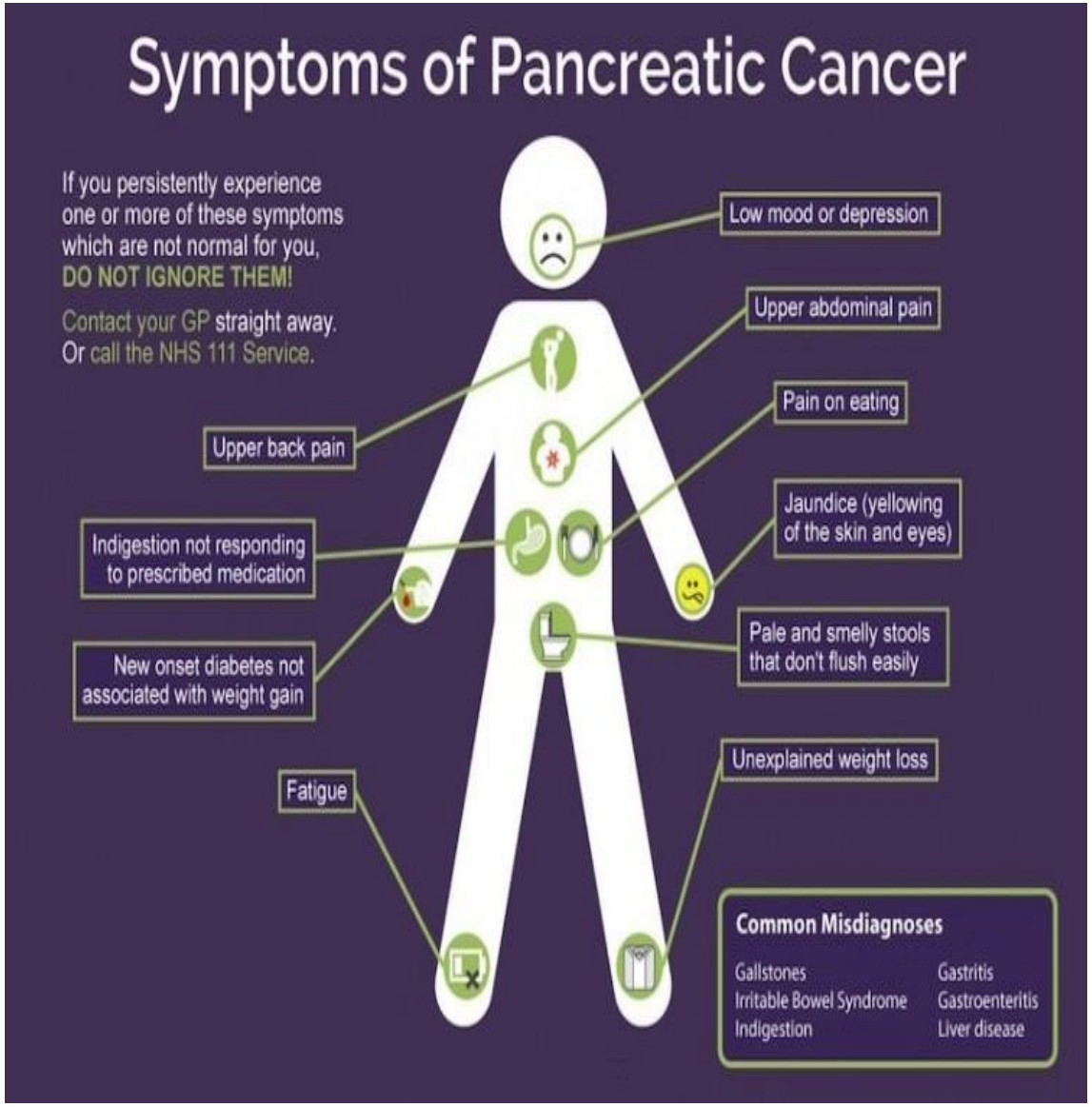
- Prognosis of exocrine Pancreas cancer is poor.
- In less than 20 % is a resection possible.
- Even after R0-resection the survival rate after 5y is less than 10 %.
- The median survival rate in palliative treatment is 6 month.
- However, chemotherapy in combination with erlotinib (Tarceva®) can increase the survival rate.

Pancreas cancer

Stage	5-year observed survival
Stage IA:	14%
Stage IB	12%
Stage IIA	7%
Stage IIB	5%
Stage III	3%
Stage IV	1%



- most patients with advanced pancreatic cancer have pain due to tumor-forming symptom.
- This reduces their daily activities



- Up to date, no therapy has a satisfactory impact on the long-term course of the disease
- Studies with gemcitabine showed marginal improvement in disease-related symptoms & prolonged 1-year survival

1997 American Society of Clinical Oncology

Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial.

H A Burris 3rd, M J Moore, J Andersen, M R Green, M L Rothenberg, M R Modiano, M C Cripps, R K Portenoy, A M Storniolo, P Tarassoff, R Nelson, F A Dorr, C D Stephens and D D Von Hoff

- The clinical benefit was 23.8% response in the gemcitabine-treated group, and
- 4.8% in the 5-FU group (P = .0022).
- Median survival was 5.65 in gemcitabine and
- 4.41 months in 5-FU group (P = .0025).
- The survival rate at 1 year was 18% for gemcitabine patients &
- 2% for 5-FU patients

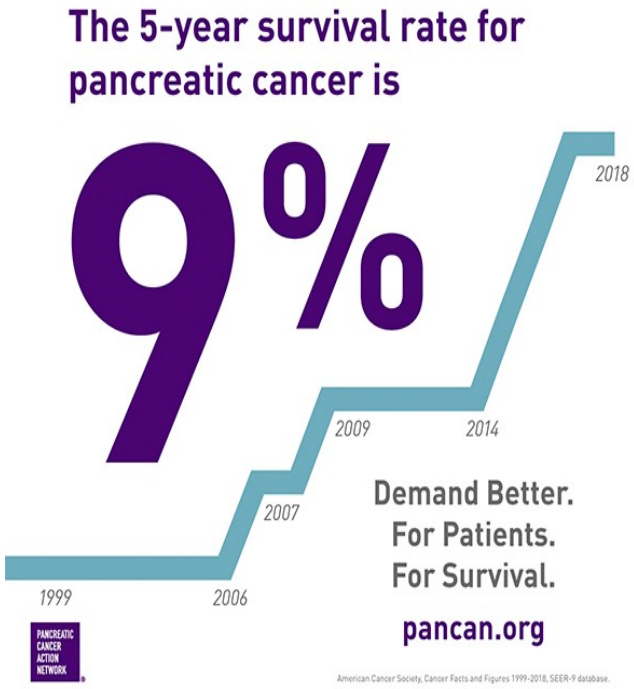
Gemcitabine in Combination With Oxaliplatin Compared With Gemcitabine Alone in Locally Advanced or Metastatic Pancreatic Cancer: Results of a GERCOR and GISCAD Phase III Trial

C. Louvet, R. Labianca, P. Hammel, G. Lledo, M.G. Zampino, T. André, A. Zaniboni, M. Ducreux, E. Aitini, J. Taïeb, R. Faroux, C. Lepere and A. de Gramont

- **Results** 326 patients were enrolled; 313 were eligible, and 157 and 156 were allocated to the GemOx and Gem arms, respectively. GemOx was superior to Gem in terms of response rate (26.8% *v* 17.3%, respectively; *P* = .04), progression-free survival (5.8 *v* 3.7 months, respectively; *P* = .04), and clinical benefit (38.2% *v* 26.9%, respectively; *P* = .03). Median overall survival (OS) for GemOx and Gem was 9.0 and 7.1 months, respectively (*P* = .13). GemOx was well tolerated overall, although a higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14.0% for GemOx *v* 3.2% for Gem), vomiting (8.9% for GemOx *v* 3.2% for Gem), and neurosensory symptoms (19.1% for GemOx *v* 0% for Gem).
- **Conclusion** These results confirm the efficacy and safety of GemOx, but this study failed to demonstrate a statistically significant advantage in terms of OS compared with Gem. Because GemOx is the first combined treatment to be superior to Gem alone in terms of clinical benefit, this promising regimen deserves further development.

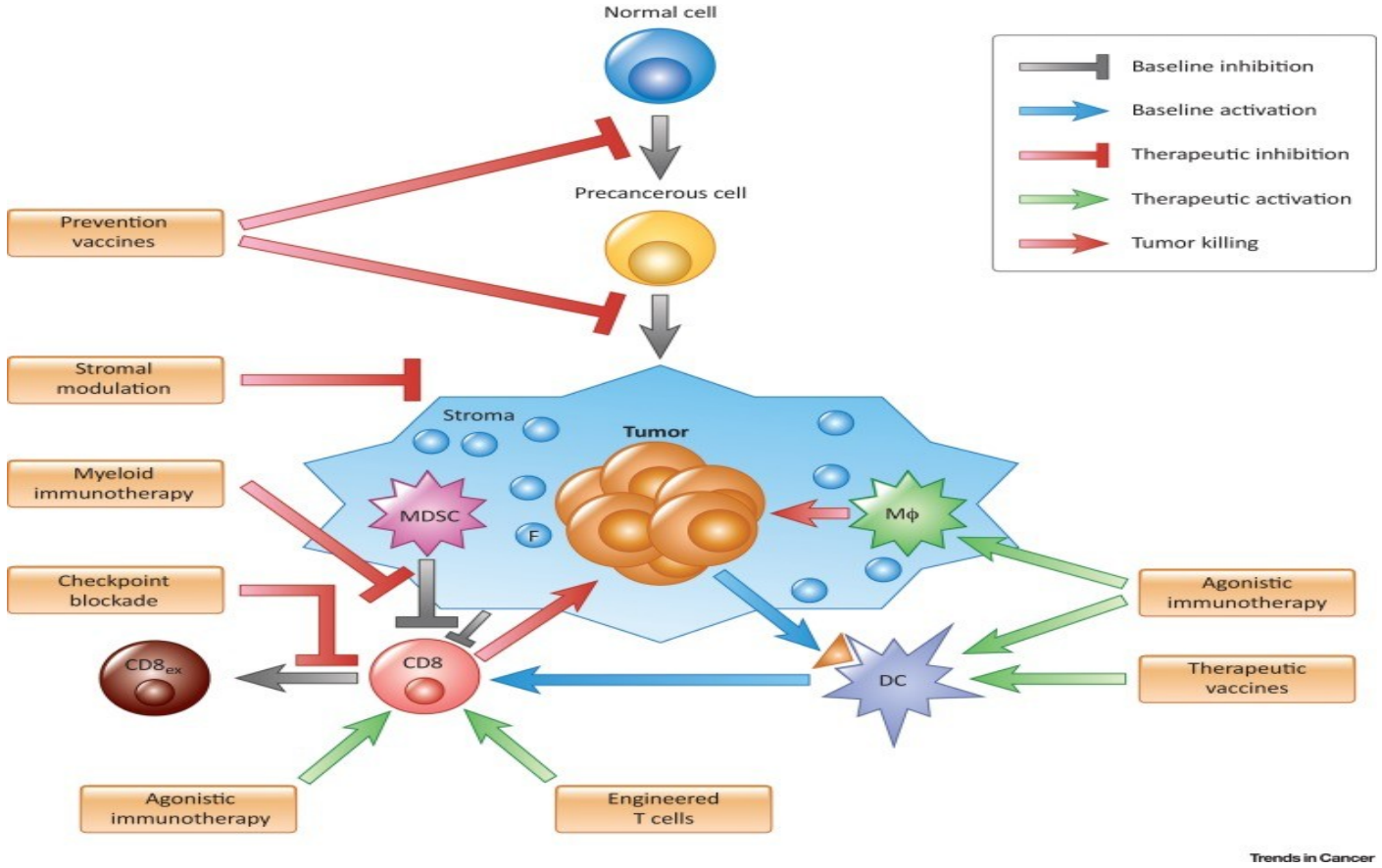
Pancreas cancer 2018

- is still one of the most aggressive malignancies, with an extremely poor prognosis.
- Therefore development of new therapeutic agents and/or modalities are neccessary to improve the clinical outcome.



- by overcoming the "multi drug resistance" (MDR)
- Use of target substances & Signal Transduction Therapy
- Molecular-genetical approach

➢ Or completely other therapy entities such as loco-regional deep hyperthermia.



Why Hyperthermia ?

- Clinical efficacy of local and regional hyperthermia has been studied and proven in numerous clinical trials.
- Randomized Phase III trials have so far been successfully completed for the combination of hyperthermia and radiotherapy & chemotherapy.

Hyperthermia: Clinical Studies

- Local hyperthermia in conjunction with radiotherapy causes significant therapeutic success
- recurrent malignant melanoma (Overgaard et al., 1995),
- In local recurrence of breast cancer (Vernon et al., 1996) and
- in advanced lymph node metastases of head and neck carcinomas (Valdagni et al., 1994).
- in advanced pelvic tumors (significant improvements in survival rates (van der Zee et al., 2000).

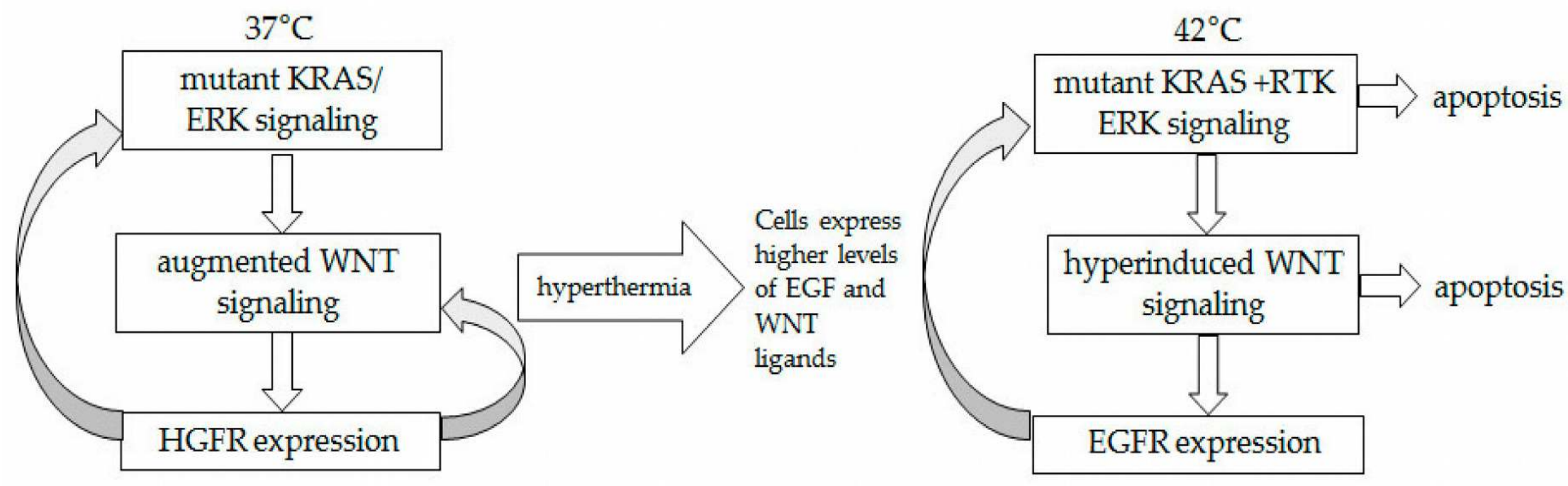
The Rationale for Combining Hyperthermia with Chemotherapy

Synergism between cytostatics & hyperthermia, e.g.

- Cisplatin & related substances,
- melphalan,
- cyclophosphamide,
- anthracyclines,
- nitrosurea,
- bleomycin,
- mitomycin C (69).

The mechanism of synergism

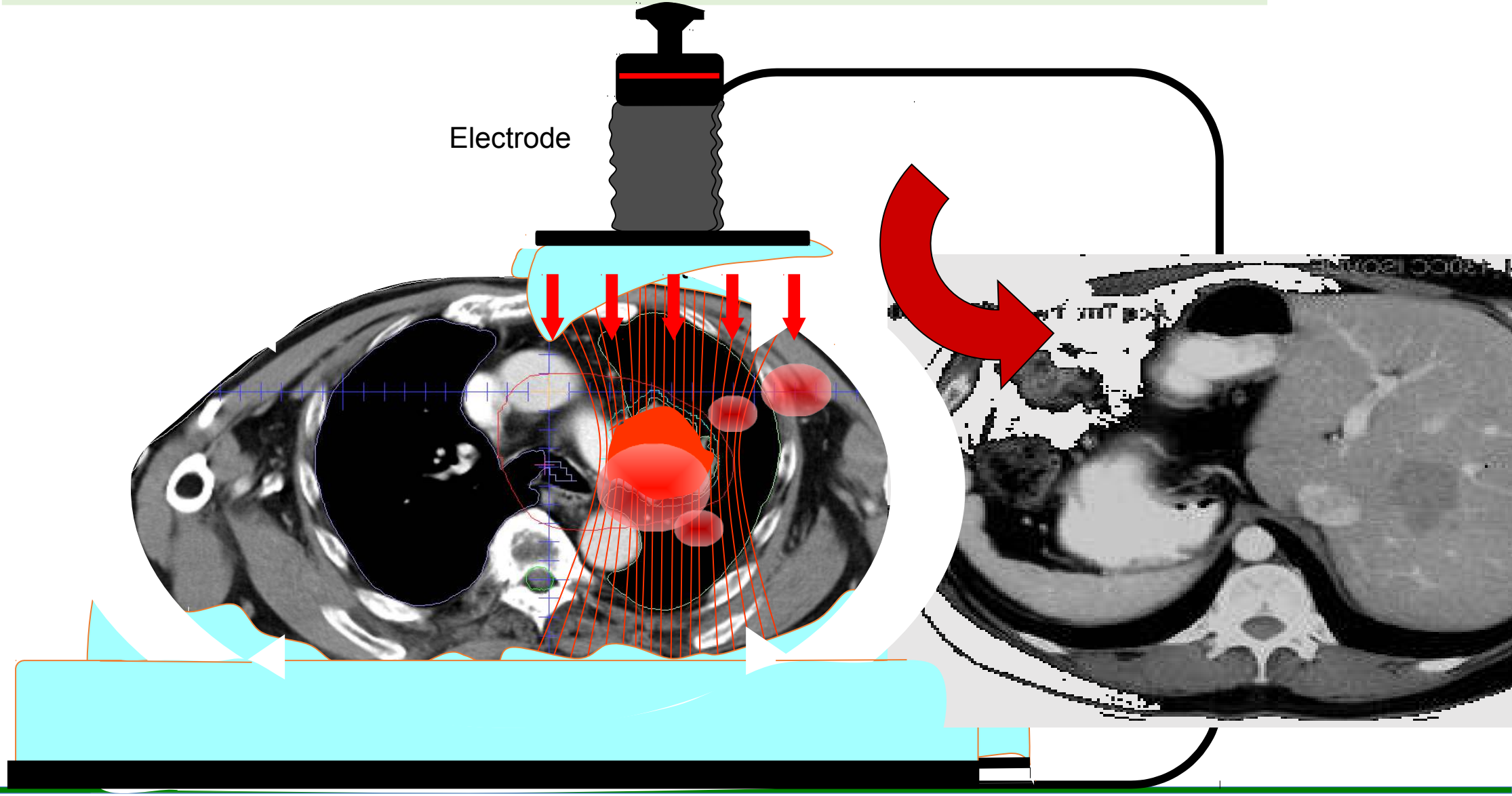
- increased cellular uptake of the drug
- increased oxygen radical production and
- increased DNA damage and
- inhibition of DNA repair (28).
- Hypoxia and pH changes are also responsible for the thermochemotherapeutic effect.


37°C
mutant KRAS/
ERK signaling
augmented WNT
signaling
HGFR expression
hyperthermia
Cells express
higher levels
of EGF and
WNT
ligands
42°C
mutant KRAS +RTK
ERK signaling
apoptosis
hyperinduced WNT
signaling
apoptosis
EGFR expression

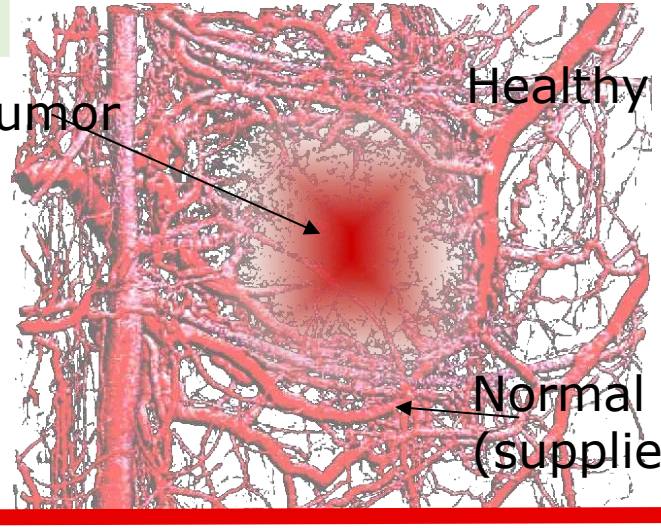
Hyperthermia has a negative effect on the proliferation of the tumor by increasing the effects of chemo- & radiotherapy and therefore on the course of the malignant disease.

Hyperthermia device for locoregional deep hyperthermia

Oncothermia – easy to use method

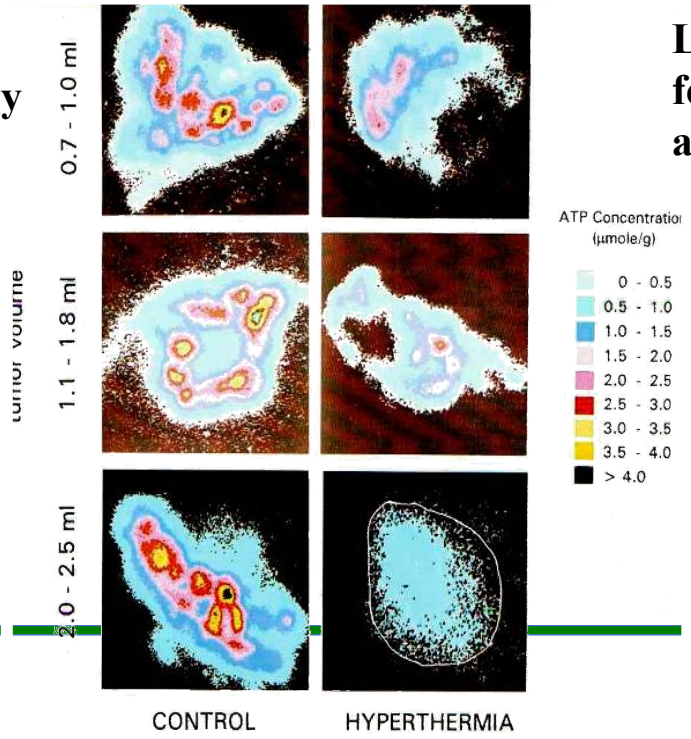


Classical hyperthermia effects

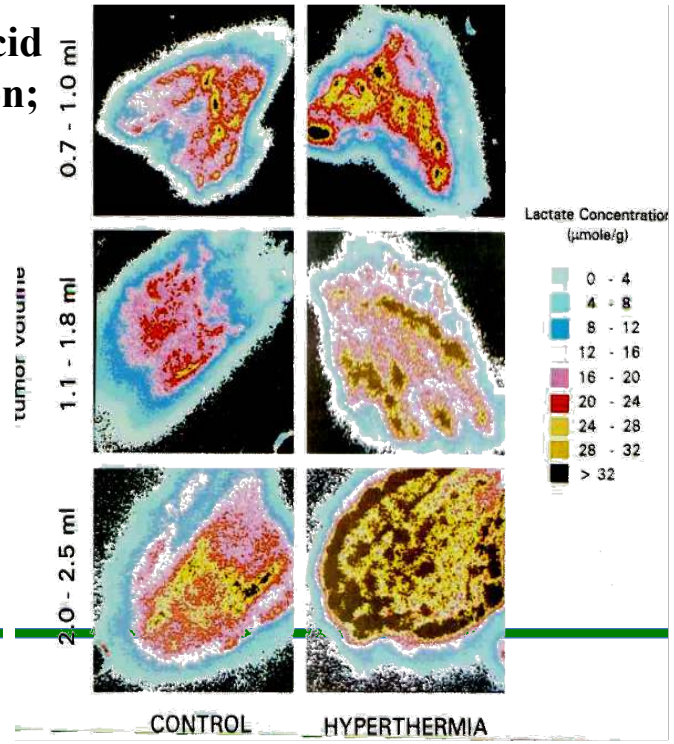


Local heating →
intensifies the metabolism, without extra supply **→ burning out**

ATP decreases; deprivation of energy



Lactic acid formation; acidosis

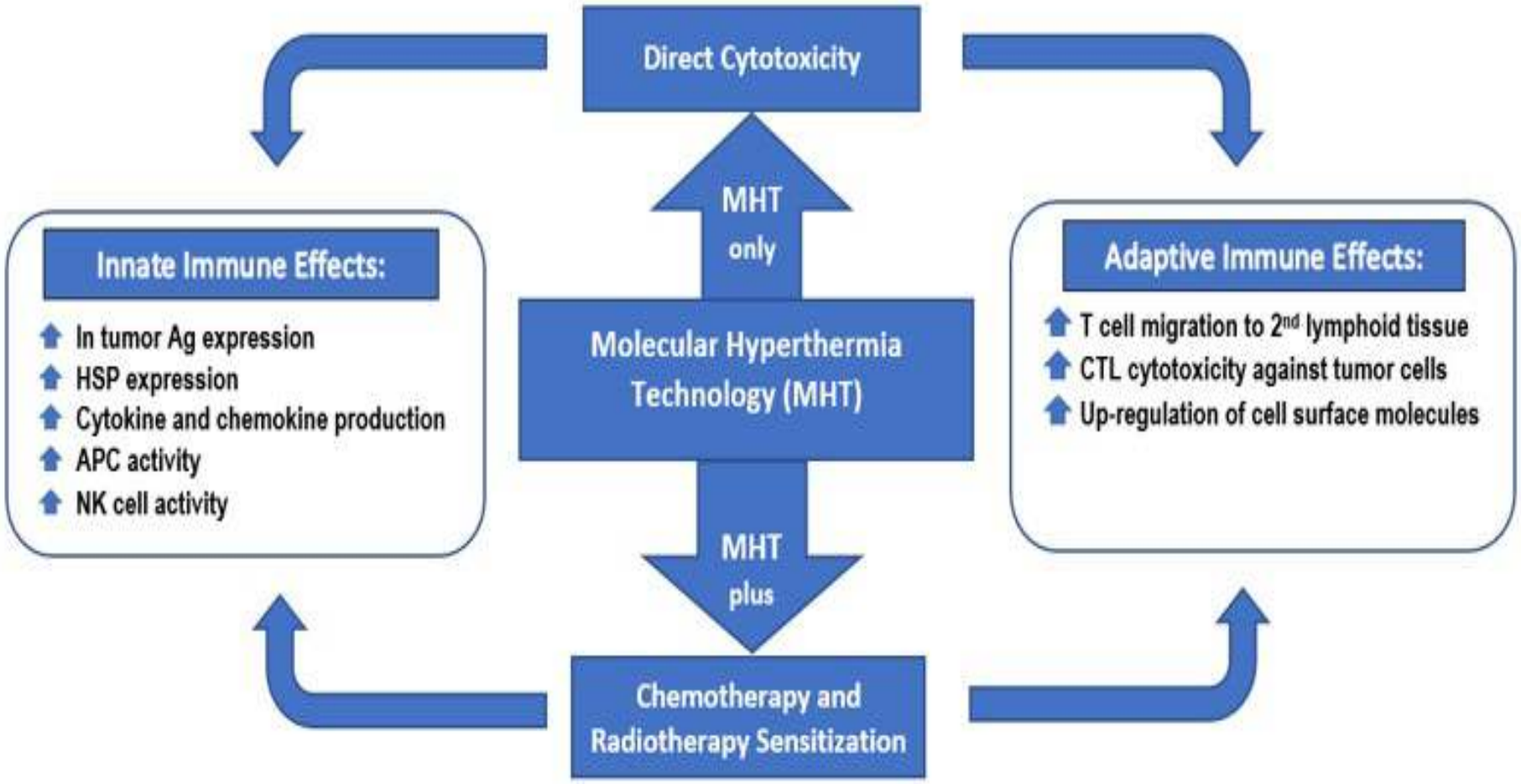


Vaupel PW, Kelleher DK: Metabolic Status and Reaction to Heat of Normal and Tumor Tissue, Thermoradiotherapy and Thermochemotherapy Vol. 1, Springer-Verlag Berlin Heidelberg 1995, pp 47-74

Hyperthermia alters tumor cells & triggers immunological activ

- From 41 ° C degrees, the tumor cell induces heat shock proteins.
- These HSPs serve as immune signals for the immune cells. e.g.
- HSP72 is a specific recognition structure for NK cells
- HSP72 increases sensitivity to the cytotoxicity of IL-2-stimulating NK cells
- Hyperthermia also leads to the activation of various cytokines, e.g. IL-1β, IL-6, IL-8, IL-10, TNF-α, G-CSF.

Hyperthermia MOA

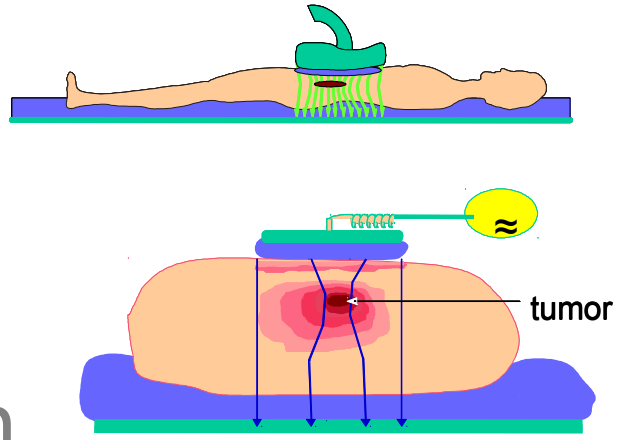


HSP – Heat shock proteins; APC – Antigen-presenting cell; NK cell – Natural killer cell; CTL – Cytotoxic T lymphocytes

Capacitive hyperthermia with radio waves (13.56 MHz) (Oncotherm 2000) was used in our study

This method combines the

- Effects of a hyperthermia with
- Effects of an electric field on tumor growth,
- Self focussing



The therapy consisted of:

1. Chemotherapy with Mitomycin C (8 mg / m2) and 5-Fluorouracil (500 mg / m2) and Folinic acid (200 mg / m2) on days 1 and 7 and
2. regional electro-hyperthermia (13.56 MHz, EHY 2000) was applied on day 1,3,5, 8,10,12, ...
3. The duration of therapy for hyperthermia was 60 min.
4. The treatment cycle was repeated every 3 weeks until progression occurred

Why did we do this ?

Due to the low response rates of a sole cytostatic therapy it should be checked:

1. whether the response to chemotherapy with mitomycin C / 5-fluorouracil / folinic acid can be increased by the use of regional hyperthermia.
2. can quality of life be improved
3. can survival time be extended

Why Mitomycin & 5-FU/ Folinic acid ?

In a randomized study with inoperable, advanced pancreatic carcinoma, an advantage of combining 5-FU with mitomycin C versus 5-FU monotherapy was demonstrated;

- The response rate was 17.6% vs. 8.4% (Maisey et al., 2002).
- There were no significant differences in survival time (6.5 months vs. 5.1 months).

Tab. 1: Patientencharakteristika

Nr.	Ge-schlecht	Alter (a)	Chemotherapie vorher	Ausgangs-stadium (AJCC)	Metastasen	Primär inoperabel
1	m	60,8		IV	hepatisch	x
2	m	71,2		IV	peritoneal	x
3	w	40,1	GEM	IV	hepatisch	
4	w	58		IV	hepatisch	x
5	m	41,1		IV	hepatisch	x
6	m	66,9		IV	hepatisch	x
7	w	37,6		IV	hepatisch	x
8	w	55,8	GEM	IV	hepatisch,	x
9	w	61,3	MITO	III	Lymphknoten	x
10	m	56	GEM	II		x
11	w	64,9		II		x
12	w	78,6		IV	hepatisch	
13	m	59,5	GEM, CDDP	IV	hepatisch, Nebeniere	
14	m	31,5		IV	hepatisch	
15	m	60,5	GEM, 5-FU, CDDP	IV	hepatisch, peritoneal	
16	m	64,8	GEM	IV	hepatisch	
17	w	48	GEM	IV	pulmonal	x
18	w	53,7		II		x
19	w	63,5	GEM, 5-FU,	IV	hepatisch	
20	m	67,2	GEM	IV	peritoneal	x
21	m	53,7	IFO	IV	hepatisch	
22	w	63,9	GEM	IV	hepatisch	
23	m	41,5		IV	hepatisch, pleural, ossär cutan	
24	m	63		IV	hepatisch	x
25	w	73,6		IV	peritoneal	x
26	m	59,2	GEM	IV	peritoneal	
27	w	60,7	MITO	II		
28	m	36		IV	hepatisch	x
29	w	60,1	GEM	IV	hepatisch	x
30	m	52,8	5-FU	IV	hepatisch, peritoneal	

Abkürzungen: CDDP = Cisplatin; 5-FU = 5- Fluorouracil; GEM = Gemzitabin; MITO = Mitomycin; 5-FU = 5- Fluorouracil; IFO = Ifosfamid;

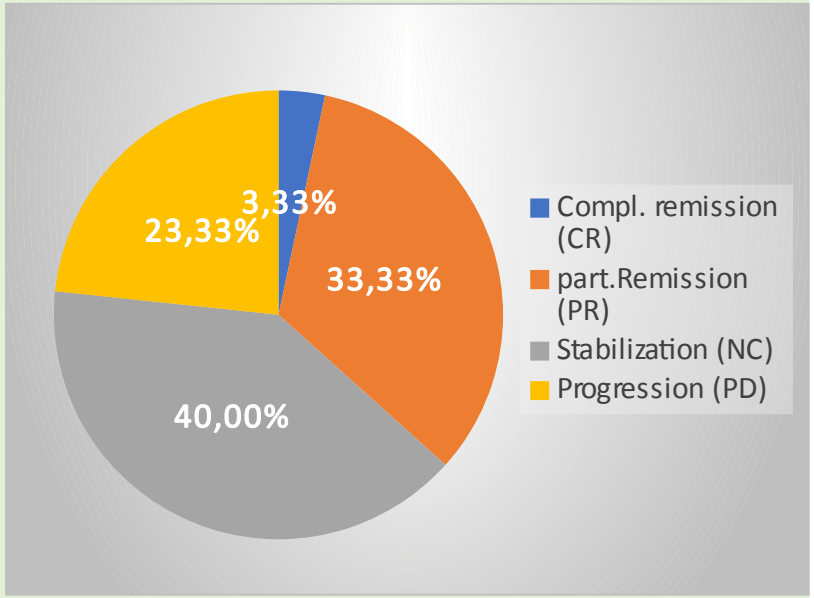
The result of this combination therapy (thermo-chemotherapy) in 30 patients (16 men and 14 women) with inoperable, widely pretreated pancreatic carcinoma was the following:

Compl. remission (CR) 1/30 = 3.33%

part.Remission (PR) 10/30 = 33.33%

Stabilization (NC) 12/30 = 40%

Progression (PD) 7/30 = 23.33%



Tab. 2: Therapieergebnisse

Nr.	Therapie-zyklen	Er-gebnis	CA-19-9-Response	Über-lebenszeit (M)	Zeit bis zur Progression (M)	Leukopenie (Grad)	Thrombopenie (Grad)	Anämie (Grad)
1	3	PR	x	6,5	2	1	2	0
2	4	PR		11	8	1	3	2
3	4	PR	x	6+	6	2	0	3
4	4	PR	x	18	7	1	0	1
5	7	PR	x	30+	26	0	0	2
6	2	PD		6	2	1	0	1
7	3	NC		15+	7+	1	2	2
8	9	NC		37	12	2	2	2
9	5	PR	x	53	10	0	0	0
10	2	PD		8	2	1	0	1
11	2	NC		4	2	1	0	1
12	3	NC		10	7	1	0	1
13	2	PR		7+	5+	2	2	2
14	5	NC		41	26	1	0	1
15	2	PD		4	3	1	0	2
16	2	NC		5	4	2	1	2
17	2	PD		5	4	0	0	0
18	2	CR		40+	40+	1	0	1
19	5	PR	x	20,5	8	2	1	2
20	5	PR		9+	8	1	0	2
21	1	PD		2	1	0	0	0
22	3	NC		7	4+	2	0	2
23	2	NC		8	6	0	0	1
24	2	NC	x	5	1,5	3	2	2
25	3	PR	x	9+	5,5	0	0	2
26	4	NC	x	8,5	8,5	0	0	3
27	1	NC		5	5	1	0	1
28	1	PD		3		0	0	3
29	3	NC		5	4	3	2	2
30	1	PD		3	2	1	0	1

Abkürzungen: PR = Partielle Remission; NC = No change (Stillstand); PD = Progression

Results

- *The median survival was 8 months (2-53)*
- *the median time to progression (1-40 months).*

Results

„Disease control rate“ (DCR)

All types of response in this study

CR, PR & SD was 72%

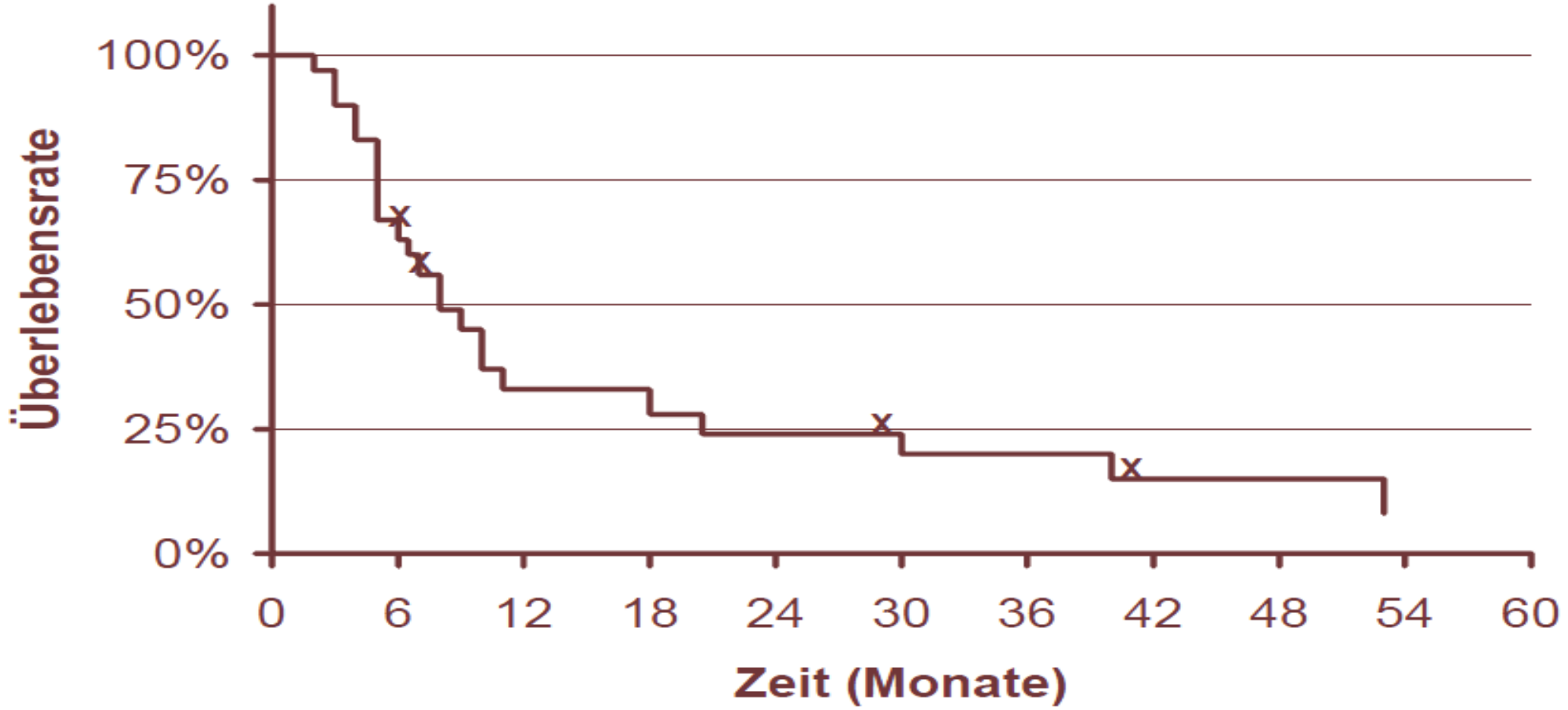


Abb. 2: Verlauf der Überlebensraten (Kaplan-Meier- Diagramm) nach Behandlung des fortgeschrittenen Pankreaskarzinoms mit Chemotherapie und regionaler Hyperthermie Tumoren darstellen (Thermo-Chemotherapie) (n= 30). Die mediane Überlebenszeit betrug 8 Monate, die 1-Jahresüberlebenszeit erstaunliche 31% und stabilisierte sich so, dass auch nach zwei Jahren noch 24% der Patienten lebten.

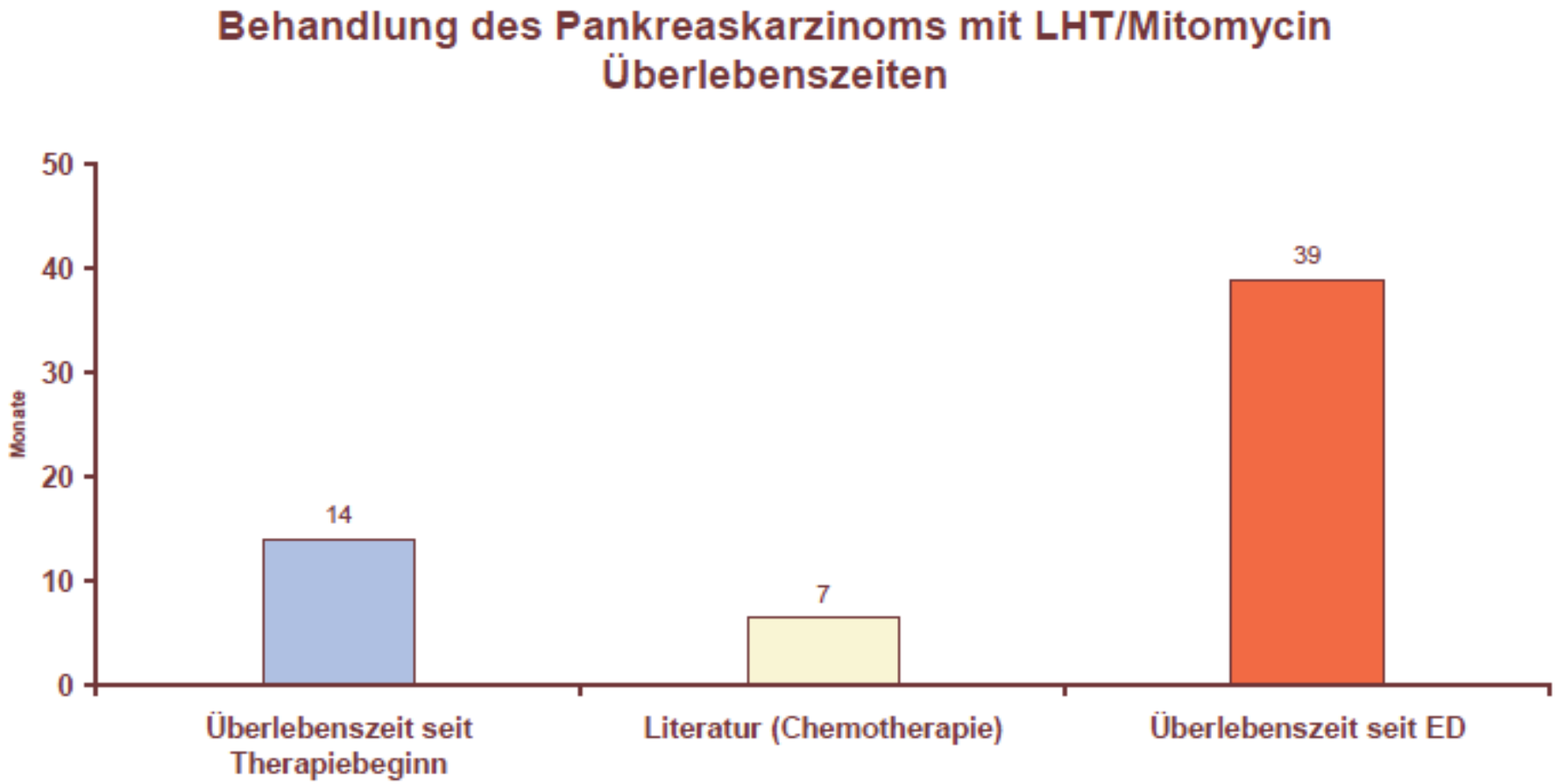


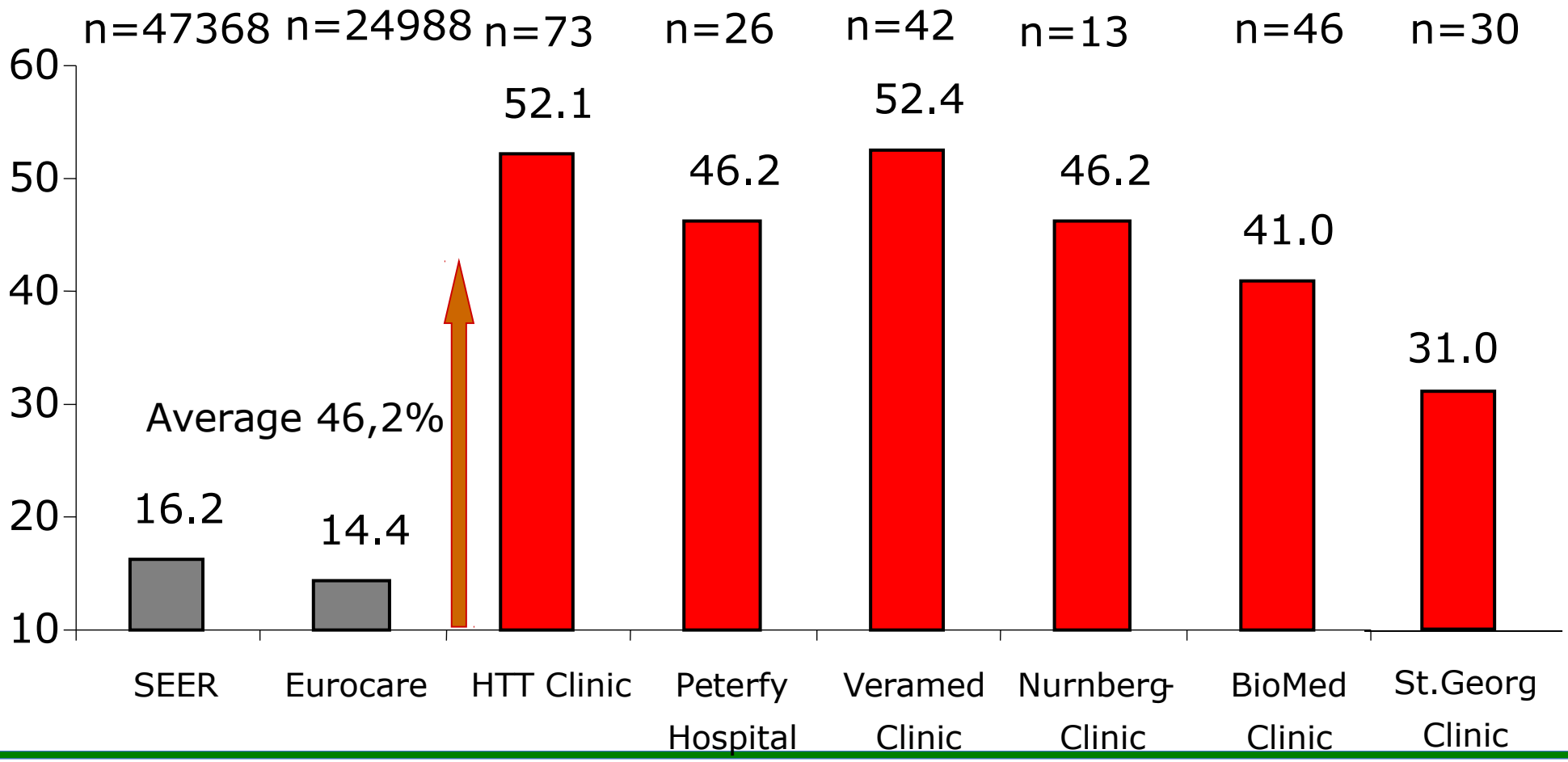
Abb. : Überlebenszeiten nach der Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und Chemotherapie (Mitomycin C).

Pancreas cancer

In this study, we were able again to show a survival advantage by combining oncothermia with chemotherapy.

Pancreas Ca 1y survival [%]

- **OER=** Oncothermia Enhancement Ratio



Patient: M. J., geb. 15.01.1946

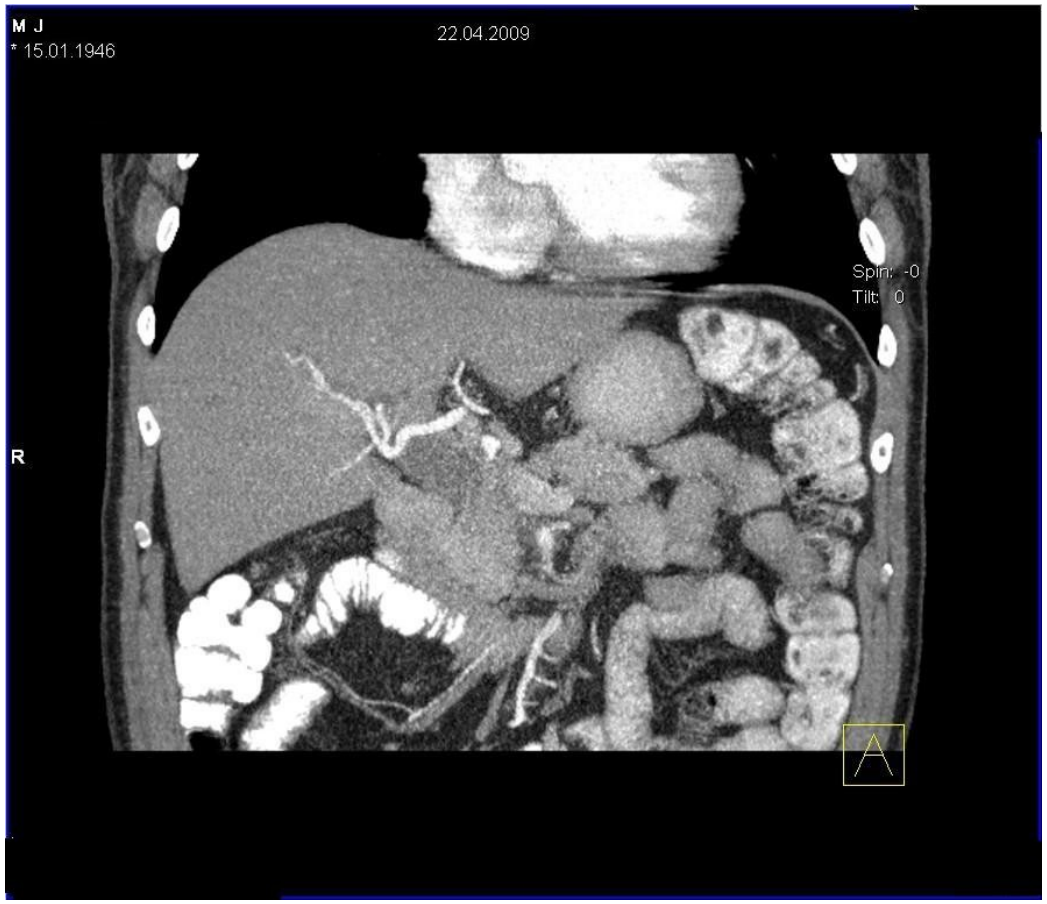
- Diagnosis: pancreatic carcinoma ED 04/09
- In addition to diagnosis:
- Cancer cachexia
- tumor anemia
- cancer pain
- History:
- In March 2009 upper abdominal pain with painless jaundice.
- In April 2009 diagnosis pancreatic-Ca. bioptically verified.

- September 2009 treatment in St. Georg clinic
- Findings: tumor cachexia (height 1.75 m, weight 55 kg, Karnofski index 60).
- Start with oncothermia 3 times a week for 60 minutes each
- Start with chemotherapy (Gemzar, Mitomycin C)
- Concomitant therapy: pain therapy, blood transfusions, parenteral nutrition
- Patient received 12 x chemo in combination with oncothermia
- The therapy was well tolerated by the patient and the weight was stable thereafter, no further blood transfusions, no more pain therapy.

CT abdomen / pelvis 22.04.2009

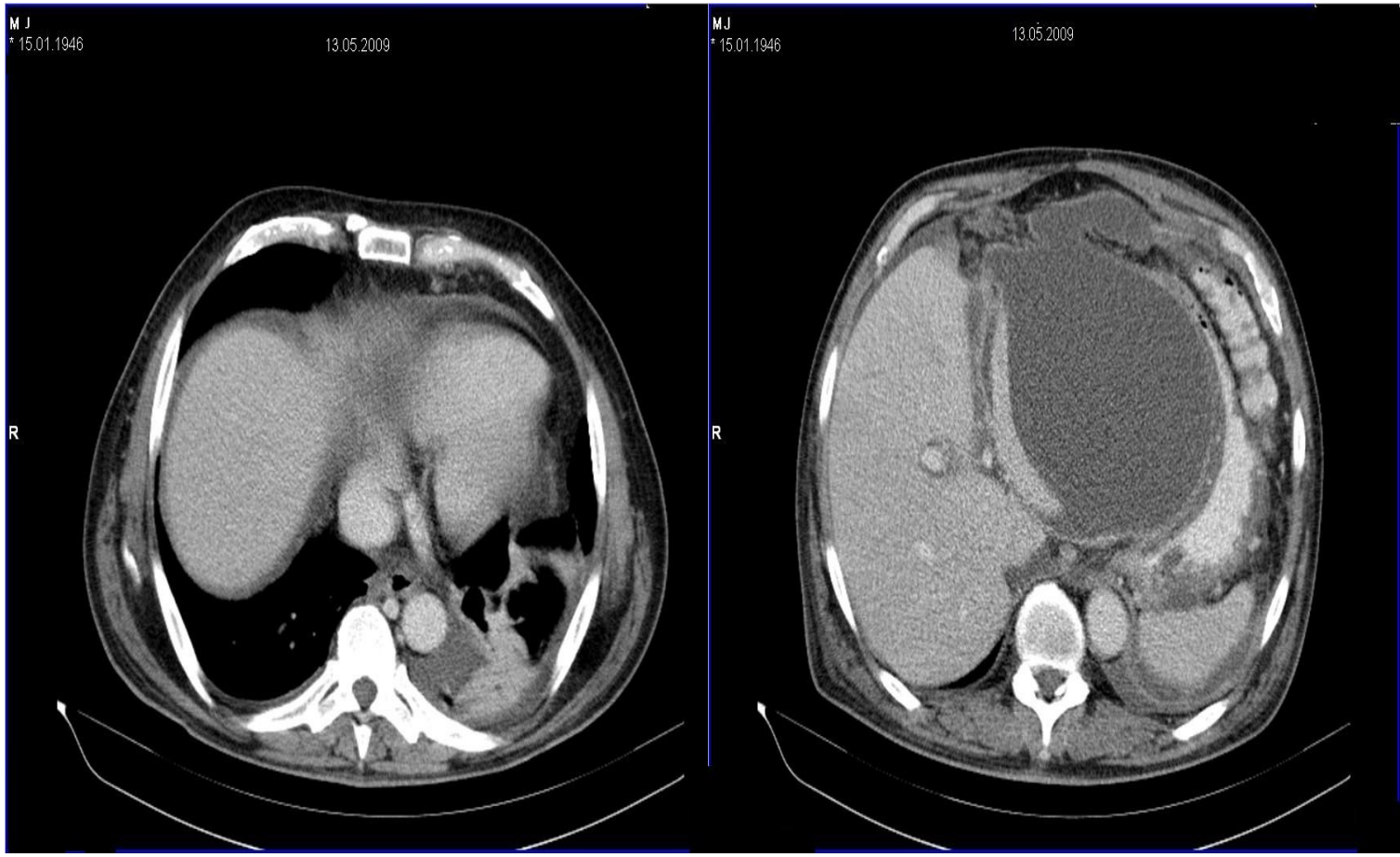
Findings:

- Pancreatic tumor at the uncinate process, with contact to the superior mesenteric artery, 2.5 cm long;
- Extended bile ducts and pancreatic duct
- locoregional lymph nodes
- otherwise no signs of organ infiltration,
- small liver cysts



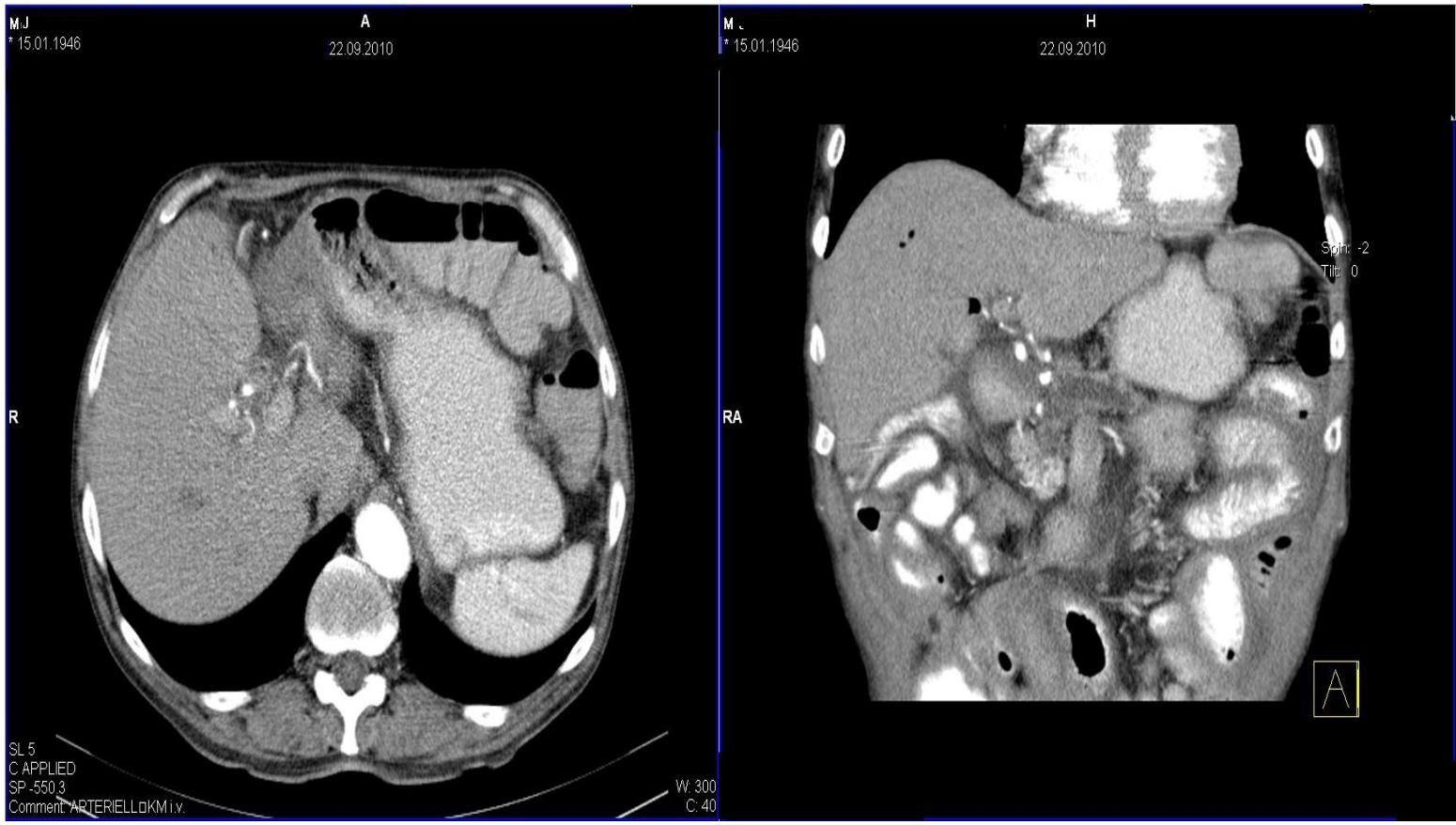
13.05.2009

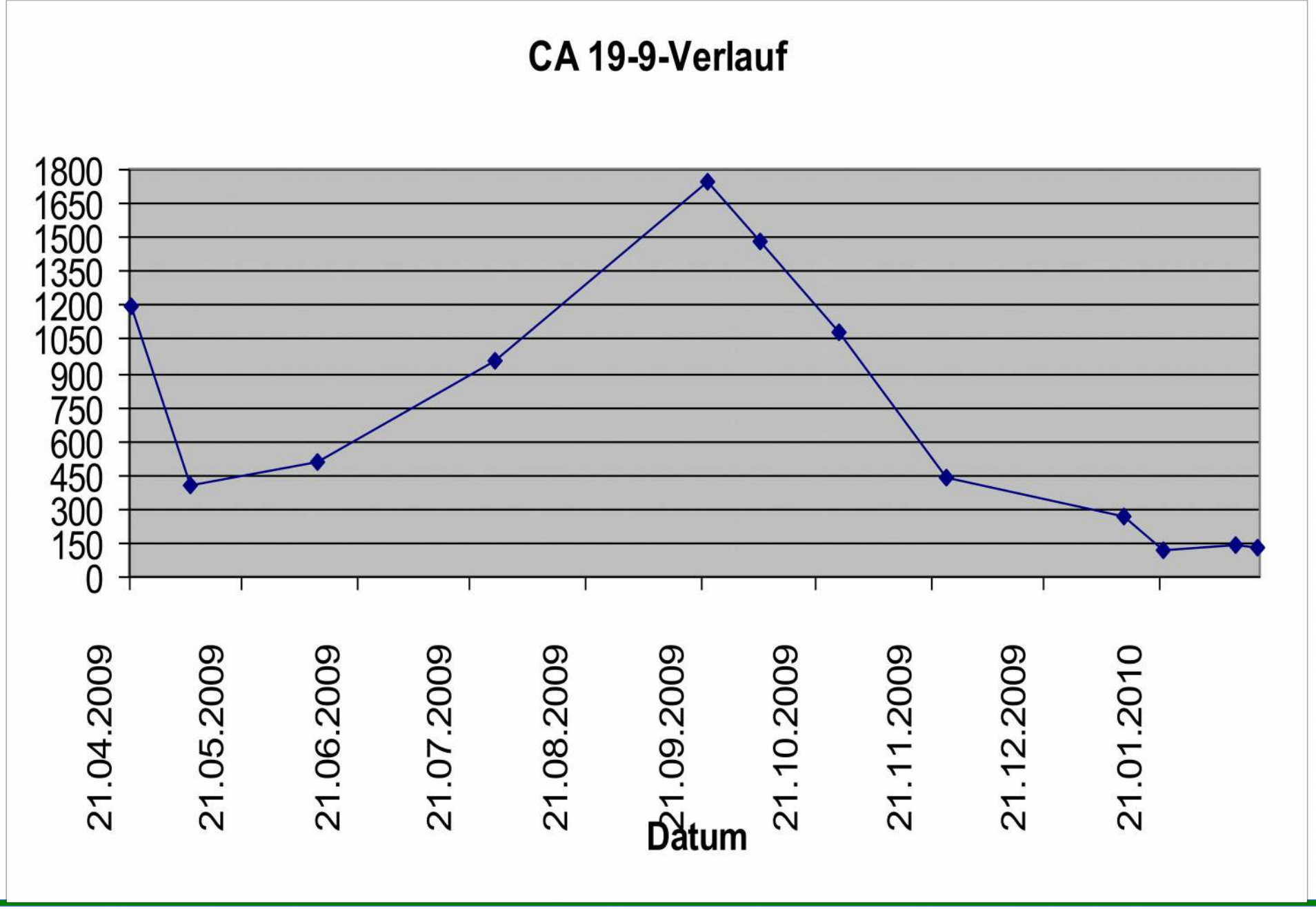
- CT abdomen / pelvis:
- large, chambered fluid behavior in the epigastrium and around the spleen
- reactive pleural effusion on the left and lung dystelectasis on the left
- free intraabdominal fluid, Z.n. cholecystectomy
- Clips detectable in the gall bladder bed
- Extent of cholestasis declined compared to the preliminary investigation
- Furthermore, pancreatic carcinoma in the uncinate process with infiltration of the surrounding fatty tissue and walling of the superior mesenteric artery, unchanged from the preliminary examination



22.09.2010 one year after beginning of therapy
CT abdomen:

- no obstruction in the intestine
- Pancreatic carcinoma largely regressed
- Bile duct stent in situ and moderate enlargement of the biliary tract




CA 19-9-Verlauf
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Conclusion: Thermo-chemotherapy of inoperable pancreatic carcinoma

- Therapy of the exocrine pancreas cancer remains one of the most difficult challenges
- Curative treatment is achieved only in a small number of the cases.
- The patients treated in our study all had an advanced stage (III or IV)
- The majority had also been treated cytostatically.
- Palliative chemotherapy with 5-FU / folinic acid and mitomycin C combined with regional radiofrequency hyperthermia was tolerated very well.

- The median survival time after thermochemotherapy was 8 months.
- Compared to results of chemotherapy in the literature, which are 3.8-6.5 months
- Where the results we achieved comparable high [4,5,18].
- The remission rate was 32% for partial and complete remissions and for stable disease (no change) another 40%.
- That means that 72% had an advantage of this treatment protokol.

It is not understandable in the face of such good results

- that hyperthermia has not spread more
- especially since it is synergistic with radiotherapy & chemotherapy
- The response rates higher and time to progression extended
- Without increasing the toxicity.

Literature

- Hyperthermia Cancer References
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- Additional credit to Erin Rurak, NMS a 4th year student at the Boucher Institute of Naturopathic Medicine (BINM - British Columbia) with specialization in integrative oncology, geriatrics, and physical medicine, and a strong passion for clinical research.

Thank you for your attention!