

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

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

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Background

The therapy results of pancreas cancer remains disappointing. In nearly all cases the disease progresses, response rates of cytotoxic therapy are low and the 5- year survival rate amounts to 1%. The purpose of our clinical study was to proof if criteria like response rate, time to progression and survival time can be improved by the use of a cytostatic treatment with Mitomycin-C, 5-FU and Folinic Acid in combination with loco-regional hyperthermia respectively by thermo-chemotherapy.

Methods

In this clinical study 30 patients with advanced pancreas cancer are included and treated with thermo-chemotherapy that is a combination of loco-regional hyperthermia and chemotherapy including Mitomycin C (8mg/m²), 5- fluorouracil (5-FU) (500 mg/m²) and calcium folinate (200 mg/m²) on day 1 and 7. Loco- regional capacitive radiofrequency hyperthermia (13.56 MHz) was applied on day 1,3,5,7,9, 11. The mean temperature achieved in the tumor site was 42°C – 44°C. Treatment was repeated every 4 weeks until progression.

Results

According to the standard criteria, 1 patient had a complete remission, 10 patients (=33,3%) had a partial remission; 12 (=40%) had a stable disease. 7 patients (=23,3%) did not respond to the therapy and showed progressive disease. Median survival time was 8 months (range 2-53 months), time to progression was 5.5 months (range 1-40 months).

Conclusion

Thermo-chemotherapy as applied in this clinical study shows a remarkable clinical outcome in advanced pancreas cancer and is well tolerated. Since all chemotherapy studies did not show significant response rates and prolongation of survival time the data obtained with thermo-chemotherapy vers positive and suggest further evaluation in randomized trials.

Key words: Thermo-chemotherapy, pancreas cancer, loco-regional hyperthermia, palliative chemotherapy, improvement of response rate & survival time

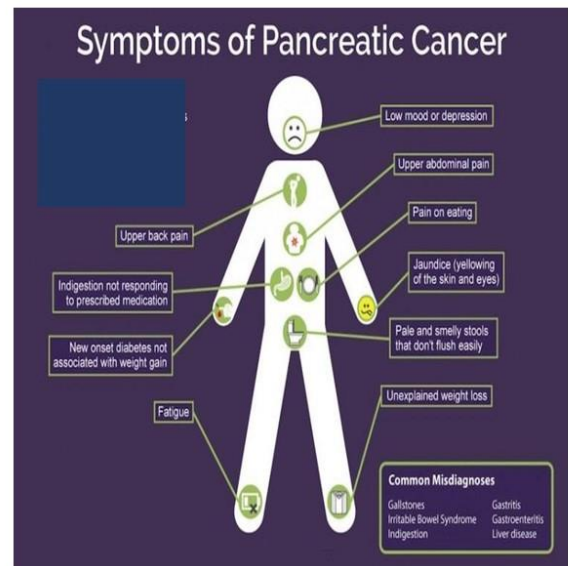
Therapy of advanced, therapy resistant Pancreas cancer, with local hyperthermia in combination with chemotherapy

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- Prognosis of exocrine Pancreas cancer is poor.
- In less than 20 % a resection is possible.
- Even after R0-resection the 5y survival rate is less than 10 %.
- **In palliative situation the median survival rate is 6 month & the 1 year survival 1-2%**

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

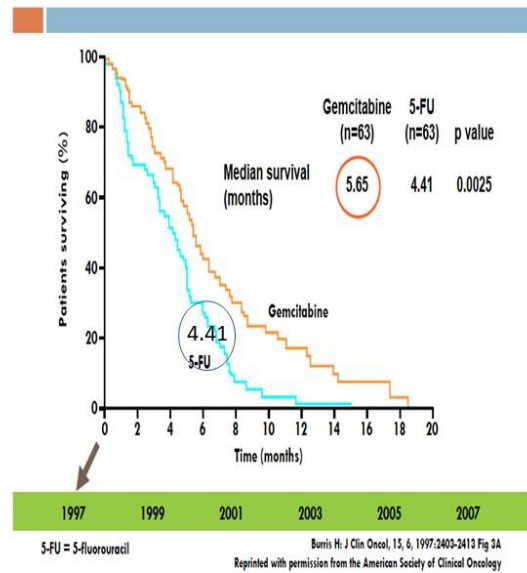


- However, chemotherapy can increase the survival rate and improve clinical symptoms
- Studies with 5-FU, Gemcitabine, Oxaliplatin, Irinotecan, Erlotinib(Tarceva) show marginal improvement in disease-related symptoms & prolonged 1-year survival

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, C D Stephens and D D Von Hoff

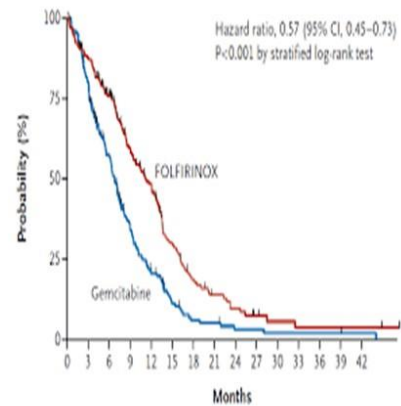
- The clinical benefit was 23.8% response in the gemcitabine-treated group, and
- 4.8% in the 5-FU group (P = .0022).
- Median survival was **5.65** in gemcitabine and
- **4.41** months in 5-FU group (P = .0025).
- The survival rate at 1 year was **18%** for gemcitabine patients & **2%** for 5-FU patients



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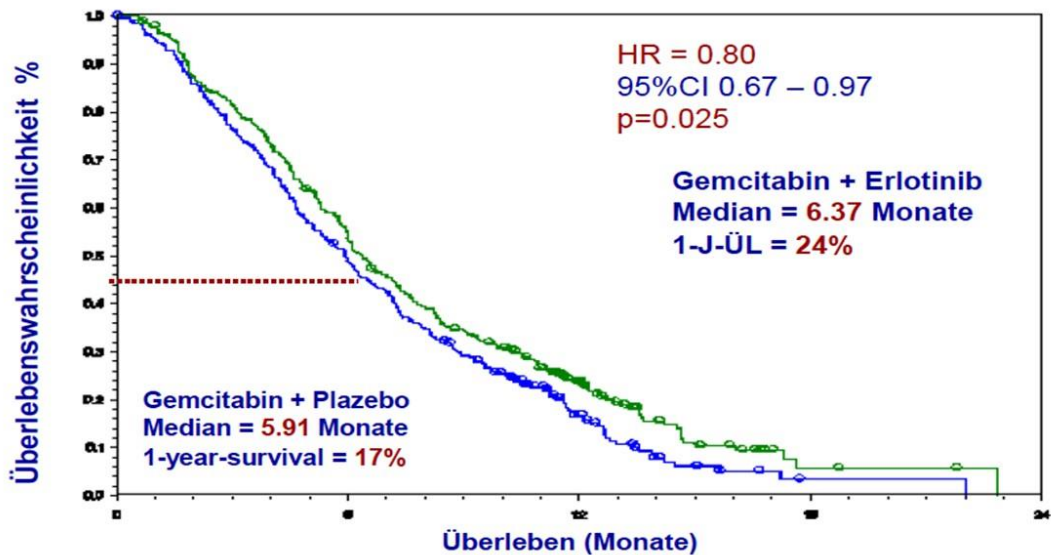
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Folfinox Gemcitabine N=171 N=171 p HR
Medianes 11.1 mo. 6.8 mo. Überleben <0.0001 0.57
1-yr. survival 48.4% 20.6%
18-mo. survival 18.6% 6%



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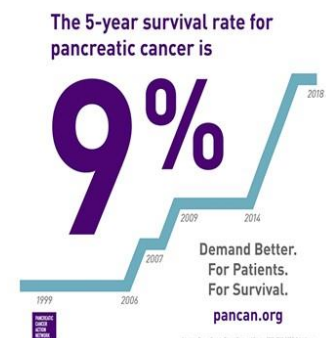
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* Adjusted for PS and extent of disease at baseline

Moore et al. JCO 2007

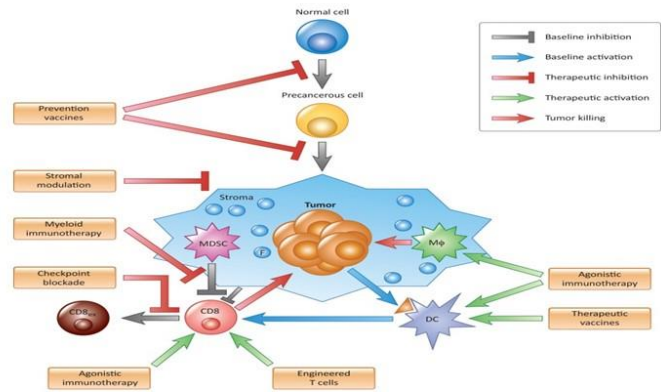
- So even in 2018 the prognosis of pancreas cancer has a poor prognosis.
- Therefore development of new therapeutic agents and/or modalities are necessary to improve the clinical outcome.



The treatment modalities under intensive research are:

- Target & Signal Transduction Therapy
- molecular-genetical & immunological approaches

➤ 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 been successfully completed for the combination of hyperthermia and radiotherapy & chemotherapy.

Local hyperthermia in conjunction with radiotherapy induced 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.

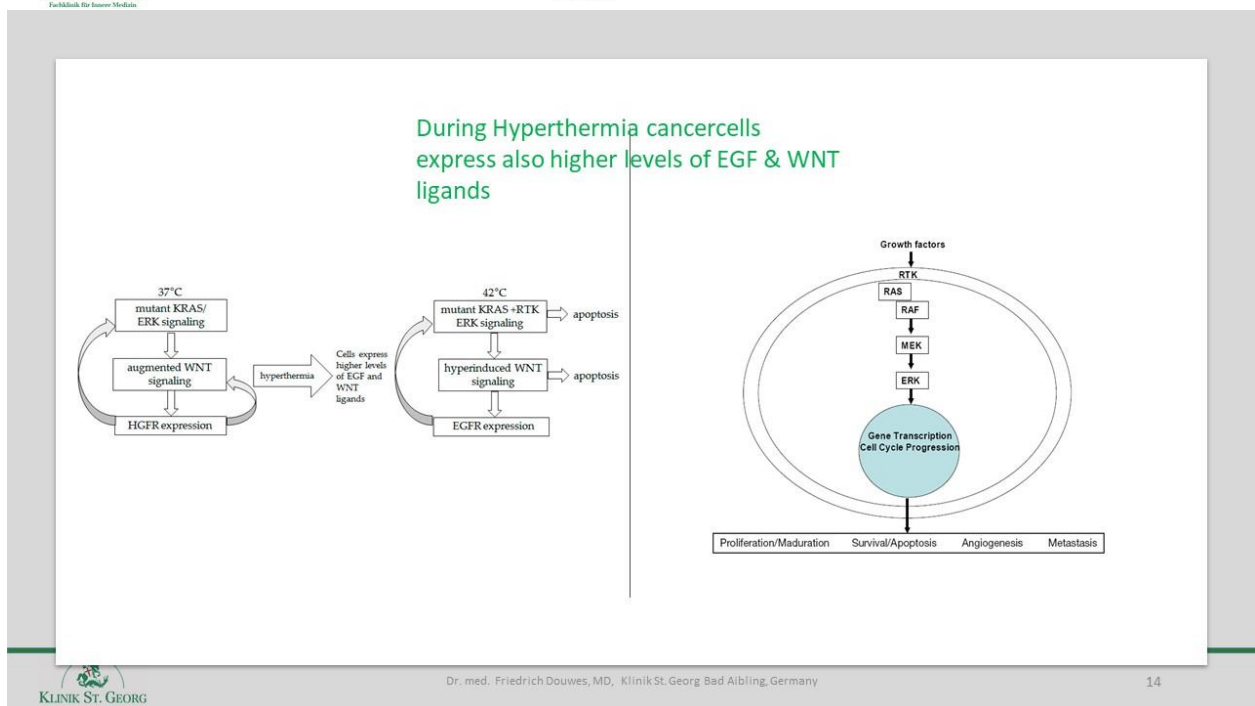
- Cisplatin, Carboplatin, Oxaliplatin
- melphalan,
- cyclophosphamide,
- anthracyclines,
- nitrosurea,
- bleomycin,
- mitomycin C (69).

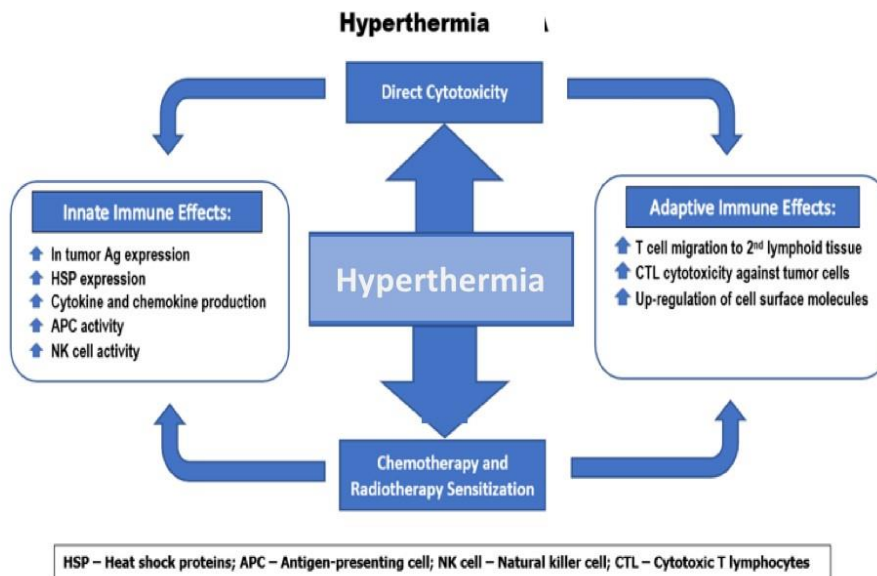


The mechanism of synergism

Heat:

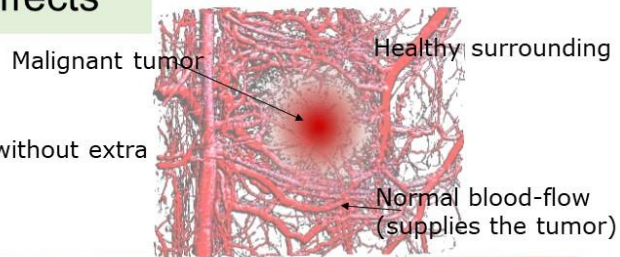
- increases cellular uptake of the drug
- increases oxygen radical production and
- increases DNA damage and
- inhibits DNA repair (28).
- Heat induce hypoxia and pH changes, which are also responsible for the higher therapeutic effect.



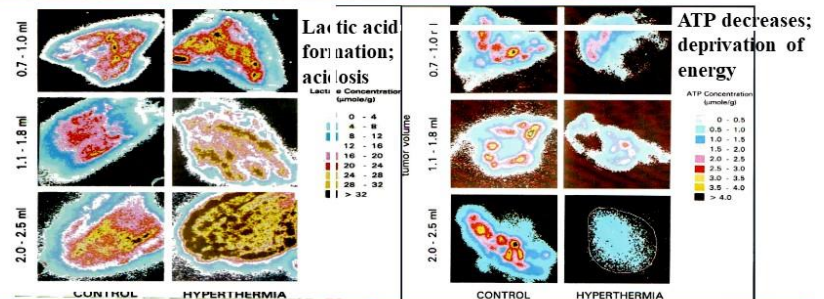
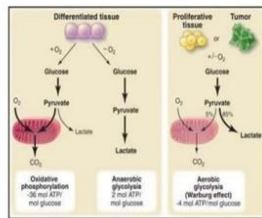


Classical hyperthermia effects

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



Comparison of Glycolysis between a Normal Tissue and Tumour/Proliferated Tissue



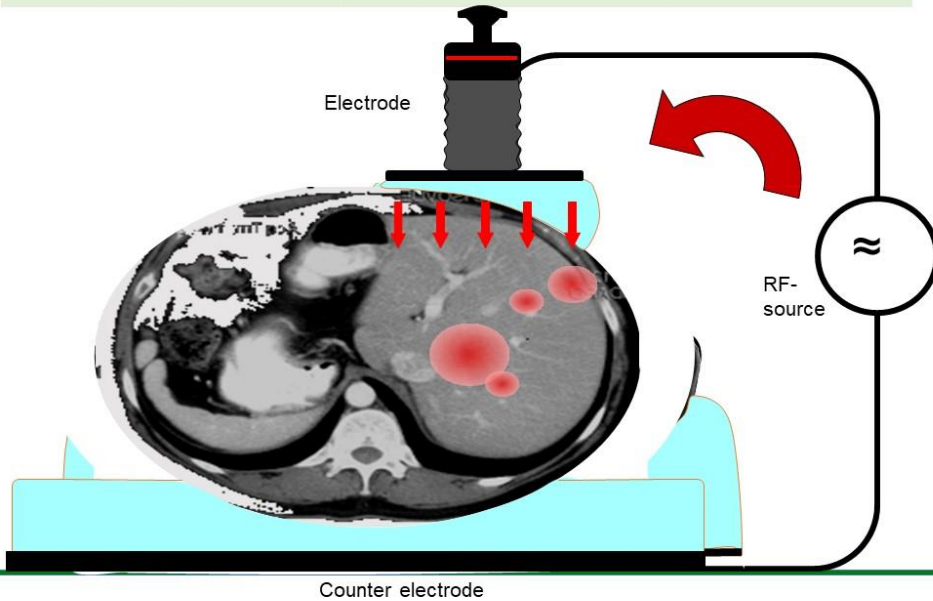
Hyperthermia alters tumorcell metabolism biology & triggers immunological activity

- 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-1 β , IL-6, IL-8, IL-10, TNF- α , G-CSF.

For our clinical trial in advance chemoresistant pancreas cancer
we used the Oncotherm device



Oncotherm – easy to use device



Our clinical trial in advance chemoresistant pancreas cancer 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 ?

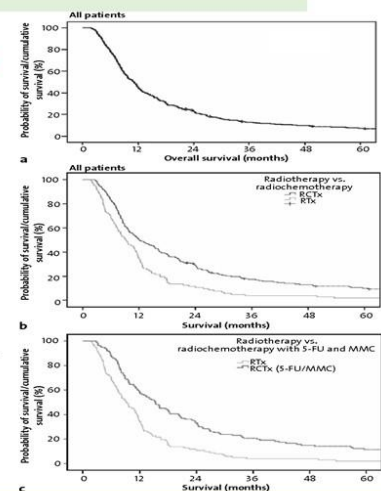
Due to the lack treatment options in such a desperate situation it should be checked:

1. whether the MDR can be overcome and if so, can a response to chemotherapy be achieved.
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).

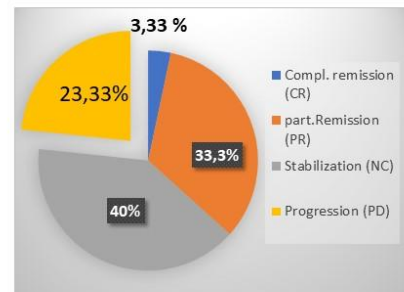


Tab. 1: Patientencharakteristika

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	
24	m	63		IV	cutan	
25	w	73,6		IV	hepatisch	x
26	m	59,2		IV	peritoneal	x
27	w	60,7	GEM	IV	peritoneal	
28	m	36	MITO	II		
29	w	60,1	GEM	IV	hepatisch	x
30	m	52,8	5-FU	IV	hepatisch, peritoneal	x

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.	Therapiezyklen	Ergebnis	CA-19-9-Response	Überlebenszeit (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	15	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	0
17	2	PD		5	4	0	0	0
18	2	CR		40+	40+	0	1	1
19	5	PR	x	20,5	8	2	0	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



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Results

- The median survival was 8 months (2-53)
- The 1 years survival 31%
- Even after 2 years still 24 % of the patients are still alive

**Disease control rate“ (DCR)
All types of response in this study
CR, PR & SD was 72%**



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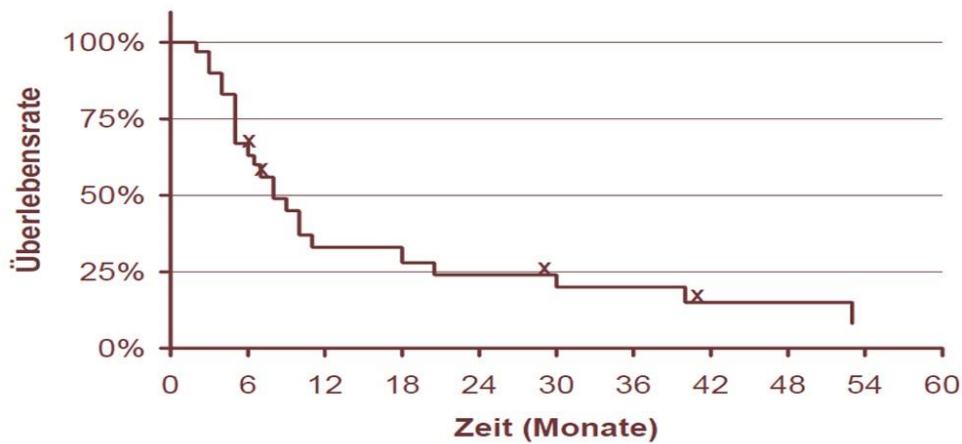
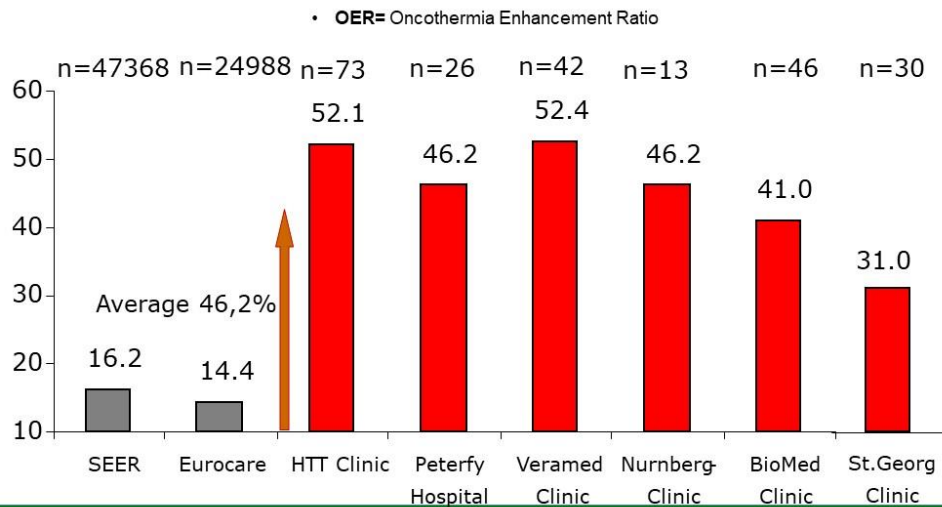


Abb. 2: Verlauf der Überlebensraten (Kaplan-Meier- Diagramm) nach Behandlung des fortgeschrittenen Pankreaskarzinoms mit Chemotherapie und regionaler Hyperthermie Tumoren darstellen (Thermo-Chemotherapie) (n= 30). Die mediane Überlebenszeit betrug 8 Monate, die 1-Jahresüberlebenszeit erstaunliche 31%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

Summary in this clinical study,

we were able to show a survival advantage in advanced MDR pancreas cancer by combining electro-hyperthermia (Oncotherm) with chemotherapy (5-FU/Mitomycin C)

Pancreas Ca 1y survival [%]



Conclusion: Thermo-chemotherapy advanced heavy pretreated pancreas 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 in our study all had an advanced stage (III or IV) and have been heavy pretreated.
- Our treatment protocol with 5-FU / folinic acid and mitomycin C combined with regional radiofrequency hyperthermia (Chemo-Thermotherapy) was tolerated very well.

Hyperthermia ideally complements:

- conventional therapies,
- increases response rates
- prolongs survival time
- improves quality of life.
- Without increasing the toxicity.



*Thank you for your
attention!*