Palliative treatment containing modulated electro-hyperthermia alone or combined with chemotherapy versus second or third line of chemotherapy in patients with advanced pancreatic cancer: a multicenter retrospective observational comparative study on 217 patients - ESHO 2023 presentation

Fiorentini Giammaria

On behalf of International Clinical Hypertermia Society Italian Network

Citation

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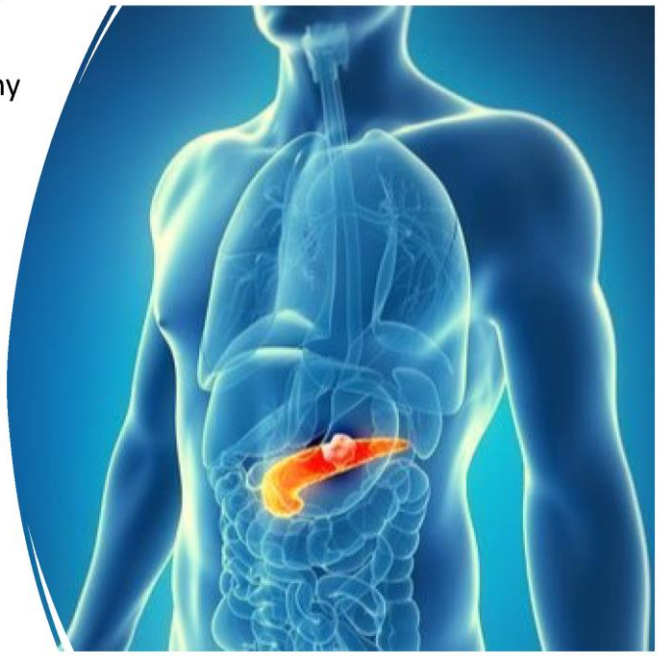
35° Annual Meeting European Society for Hyperthermic Oncology

26-29 September 2023- Cologne, Germany



Palliative treatment containing modulated electro-hyperthermia alone or combined with chemotherapy versus second or third line of chemotherapy in patients with advanced pancreatic cancer: a multicenter retrospective observational comparative study on 217 patients

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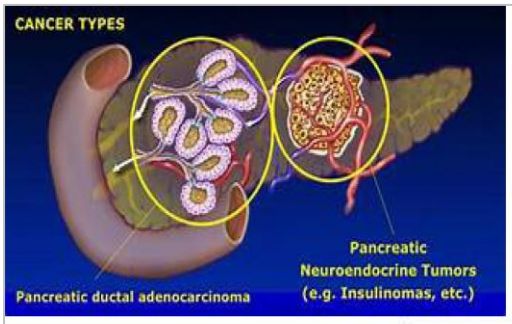
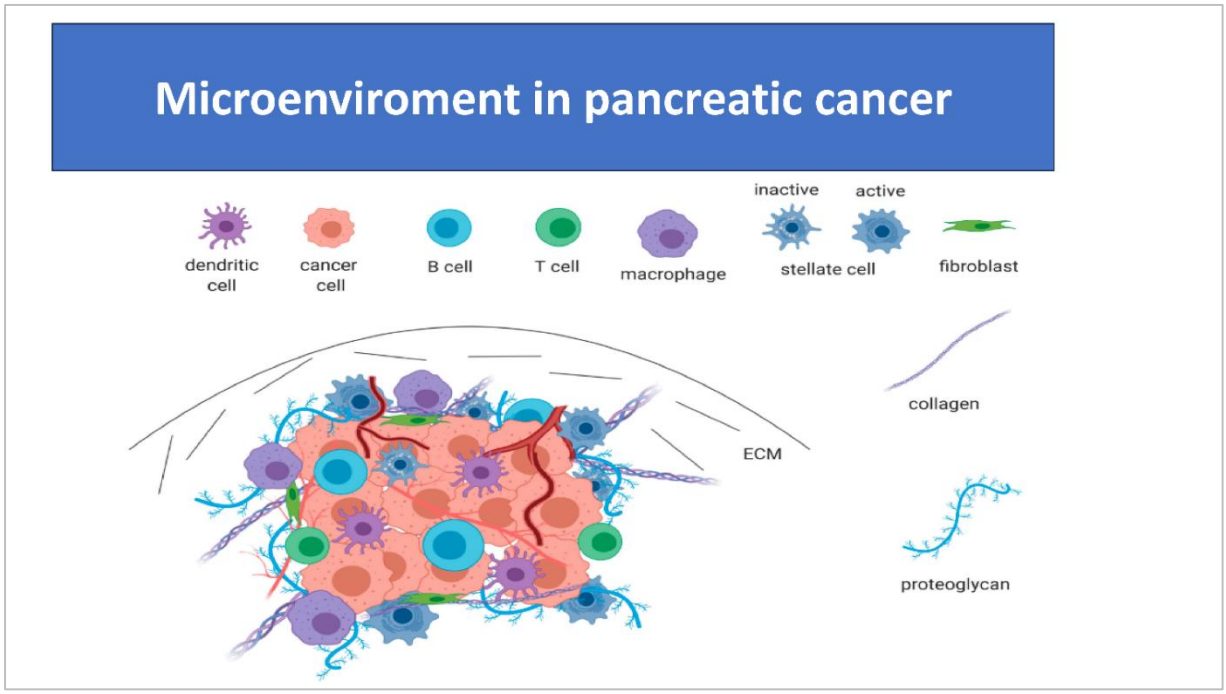
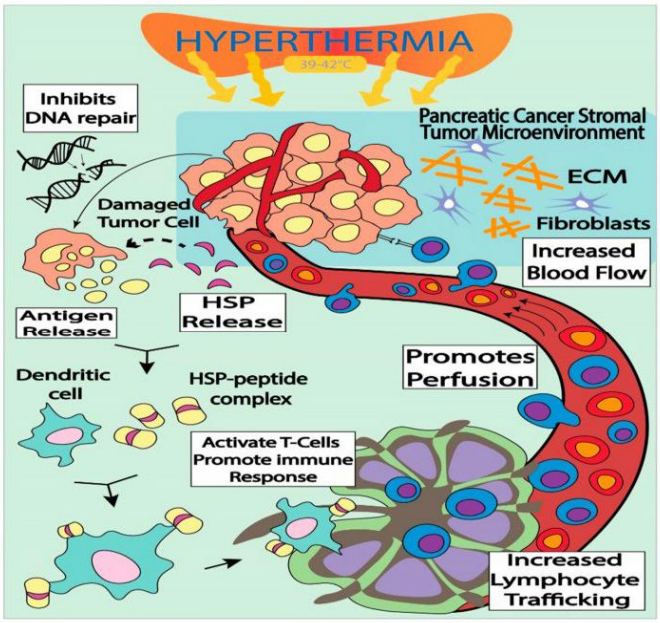


Istology : all patients treated are adenocarcinoma

Stage of cases treated in our study

stage	TNM classification	clinical classification (in terms of treatment)	median survival (months)
0	Tis, N0, M0	resectable	
IA	T1, N0, M0	resectable	24.1
IB	T2, N0, M0	resectable	20.6
IIA	T3, N0, M0	resectable	15.4
IIB	T1/2/3, N1, M0	locally advanced potentially resectable	12.7
III	T4, N0/1, M0	locally advanced unresectable	10.6
IV	T1/2/3/4, N0/1, M1	metastatic	4.5


Microenviroment in pancreatic cancer
dendritic cell
cancer cell
B cell
T cell
macrophage
inactive
active
stellate cell
fibroblast
ECM
collagen
proteoglycan


HYPERTHERMIA
39-42°C
Inhibits DNA repair
Damaged Tumor Cell
Antigen Release
HSP Release
Dendritic cell
HSP-peptide complex
Activate T-Cells Promote immune Response
Pancreatic Cancer Stromal Tumor Microenvironment
ECM
Fibroblasts
Increased Blood Flow
Promotes Perfusion
Increased Lymphocyte Trafficking

Rationale from praevious studies :

The clinical benefit of hyperthermia in pancreatic cancer: a systematic review

Astrid van der Horst, Eva Versteijne, Marc G. H. Besselink, Joost G. Daams, Esther B. Bulle, Maarten F. Bijlsma, Johanna W. Wilmink, Otto M. van Delden, Jeanin E. van Hooft, Nicolaas A. P. Franken, Hanneke W. M. van Laarhoven, Johannes Crezee & Geertjan van Tienhoven

Conclusions: Hyperthermia, when **added to chemotherapy and/or radiotherapy**, may positively affect treatment outcome for patients with pancreatic cancer. However, the quality of the reviewed studies was limited and future randomized controlled trials are needed to establish efficacy (2018).

International Journal of Hyperthermia

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METHODS

This was a **multicenter retrospective observational comparative study**; data were collected for **patients with stage III-IV pancreatic cancer** that were **treated with mEHT alone or** in **combination with CHT from 2003 to 2021**

→ A total of 628 patients were treated in nine Italian Hospitals

→ 217 of them were included in this study

→ 89 (41%) of them received mEHT ± CHT (mEHTgroup)

→ 128 (59%) with CHT (no-mEHT group)

CHT was mainly gemcitabine-based regimens in both study groups

mEHT protocol and device

→ was performed using the EHY-2000plus device (CE0123, Oncotherm, Torisdorf, Germany)

→ applying a radiofrequency current of 13.56 MHz as carrier frequency that was modulated by time-fractal fluctuation

→ The energy was transferred by capacitive coupling, with precise impedance matching

The hyperthermia protocol included

→ three mEHT treatments/week for 2 mo

→ starting at a 60 W power for 40 min

→ Following treatments were performed by increasing the power up to 150 W and the time up to 90 min in 2 wk.

mEHT was administered **after CHT or within 48 h**, in order to **couple the high drug blood concentration** with the **modulated electro hyperthermia** and **optimize their synergy**

Patients: sites of metastases

SITE	Total	mEHT 89		no-mEHT 128			P
LIVER	132	70	53%	63	51%		n.s.
Peritoneum	55	35	27%	20	%19		n.s.
Lymphnodes	37	22	17%	15	15%		n.s.
OTHER	10	5	4%	5	5%		n.s.

Patients: praevious treatments

Patients	Total 217	mEHT 89		no-mEHT 128			P
Metastatic	142	70	79%	72	56%		0.004
RT	10	1	1.1%	9	7%		n.s
CHT	136	68	76%	68	53%		0,005
Surgery	51	22	24%	31	24%		n.s.

RESULTS:

→ Overall survival and progression free survival

- Overall survival (20 mo, range 1,6-24 *vs* 9 mo, range 0,4-56.25, $P < 0.001$)
- progression-free survival (7 mo, range2-24 *vs* 5 mo, range 0.4-41, $P < 0.05$)
- OS and PFS were **better for the mEHT+CHT group** compared to the CHT group.

RESULTS: Tumor response and Safety

Tumor response at three month follow up was available for:

- 87(98%) of mEHT
- 111 (88%) patients for non-mEHT group

→ mEHT patients showed a higher number of PR (45% vs 24%, P= 0.0018) and a lower number of progressions (PD) (4% vs 31%, P <0.01) than no-mEHT group

→ SD had similar value in both groups: 51% for mEHT and 45% for no-mEHT

→ Median mEHT sessions was 16.8 (range 6-25), resulting 1495 mEHT delivered sessions.

Tumor response at 3 months

	mEHT	N=87	no-mEHT	N=111	
	n	%	n	%	p
PR	39	45	27	24	0,0018
SD	44	51	50	45	0,8430
PD	4	4	34	31	<0,001

Side effects and toxicity

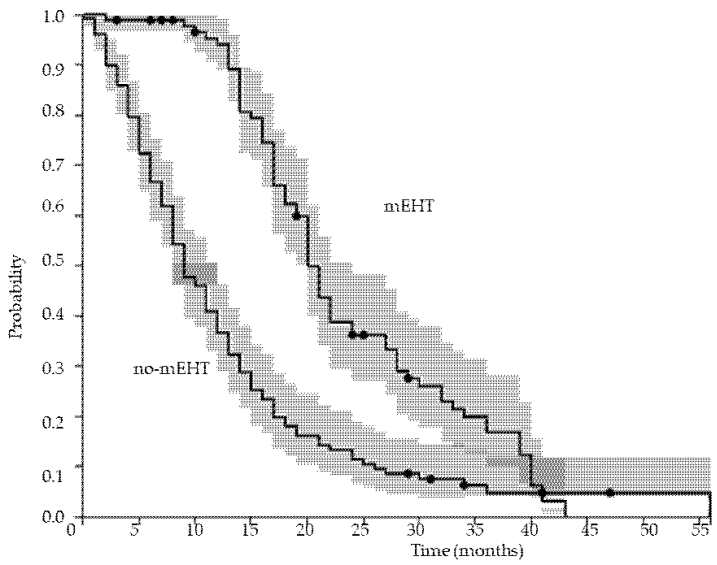
→Adverse events were reported in 2.6% of cases and included:

- G1 skin pain in 22 (1.5%) sessions
- G1-2 burns in 16 (1.1%) cases that resolved in few days

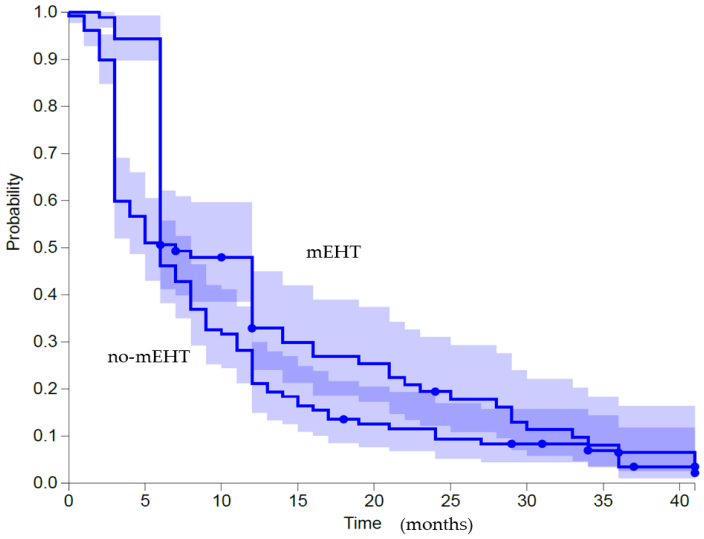
mEHT **did not increase** haematological, hepatic, pulmonary and metabolic toxicity due to CHT

Particularly no increased blood pressure or any other cardiac changes after adequate cardiological monitoring

OS of mEHT and no-mEHT groups. Dots represent censors, cloud area represent CI 95%.



PFS of mEHT and no-mEHT groups. Dots represent censors, cloud area represent CI 95%.



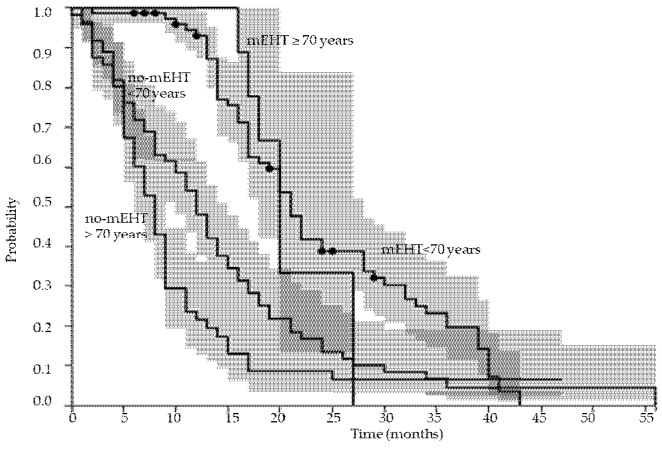
OS of mEHT and no-mEHT groups divided by age. Dots represent censors, cloud area represent CI 95%

The analysis of OS **by age less 70 years or more 70 years** showed that:

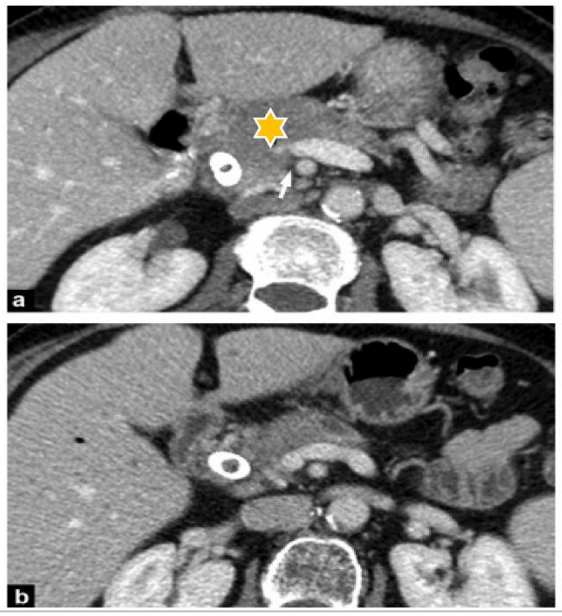
→ there was no difference in OS between mEHT less than 70 years (20 mo, range 2-43 m) and more 70years (20mo , range 3-27) P=0.235

→ whereas no-mEHT **patients with less than** 70 years had a higher OS than no-mEHT more than 70 years group (12 mo, range 1-56 vs 8 range 1-47, P= 0.01)

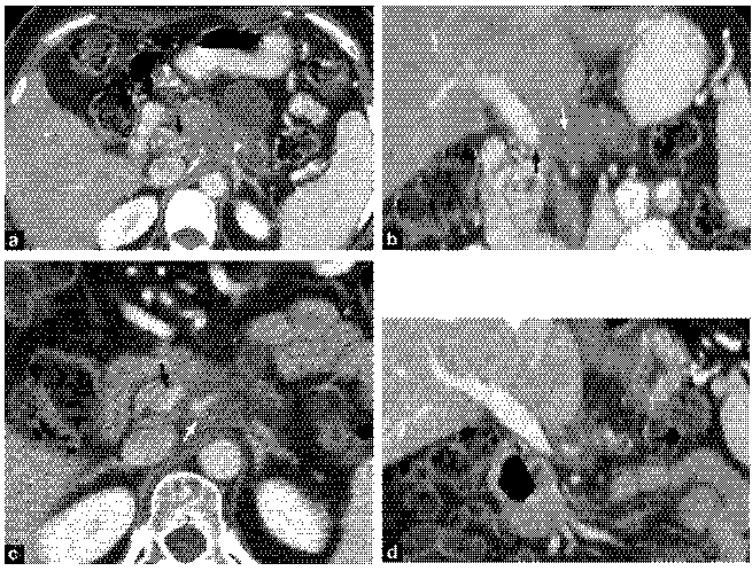
→ mEHT had a longer OS than no-mEHT group both among less than 70 years (20 mo range 3-27 vs 8 mo range 1-47, p <0.01) and more than 70 years (20 mo range 2-43 vs 12 mo range 1-56, P<0.01).



PT 33-PANCREATIC CANCER (HEAD) AFTER DRAINAGE RECEIVED MEHT (28 SESSIONS) PLUS GEM 9 C.
SEE EVIDENCE OF RESPONSE



PT 26 - PANCREATIC CANCER (BODY) PROGRESSED AFTER 6 C. OF GEMOX,
RESPONSE AFTER MEHT+ GEM (32 MEHT SESSIONS AND 8 C. OF GEM)



LOCOREGIONAL HYPERTHERMIA: SOME of ONGOING STUDIES IN PANCREATIC CANCER

1. **NCT01077427: Hyperthermia European Adjuvant Trial (HEAT) in pancreatic cancer University Munich (Germany)**
2. **NCT02862015: Multicenter RCT of the Clinical Effectiveness of Oncothermia With Chemotherapy in Metastatic Pancreatic Cancer Patients. University Seul (S. Korea)**
3. **NCT02150135: Effect of Oncothermia on Improvement of Quality of Life in Unresectable Pancreatic Cancer Patients. University Seul (S. Korea)**
4. NCT00178763 **Hyperthermia With Chemotherapy for Locally Advanced or Metastatic Pancreas Cancer (Texas)**
5. NCT02439593 **Concurrent Hyperthermia and Chemoradiotherapy in LAPC: Phase II Study (HEATPAC; Zurig, Swiss)**
6. NCT04889742 **Hyperthermia Enhanced Re-irradiation of Loco-regional Recurrent Tumors (HETERERO) Berlin, Germany**

Take Home Massage

→ The addition of mEHT to systemic CHT **improved overall and progression-free survival** and **local tumor control** with comparable toxicity

→ On the basis of this study and the other numerous studies in the literature, and the the ongoing trials it now seems time to organize an international randomized trial to evaluate the utility of electro-hyperthermia in this serious disease