Modulated electro-hyperthermic treatment in the therapy of inoperable pancreatic cancer patients - a single center case-control study

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Abstract

Introduction: Inoperable pancreatic cancer poses a challenge as it is often a therapy resistant tumor which bears a poor prognosis. Hyperthermic treatments aim to break this resistance and facilitate oncotherapies.

Objective: To analyze the benefit of concomitant mEHT for inoperable pancreatic cancer patients to form basis for further investigation.

Materials and methods: We present a retrospective single-center case-control study including 78 inoperable pancreatic cancer patients. The case group comprised 39 patients receiving first mEHT treatment at Semmelweis University Cancer Centre between 2016 September and 2019 November and underwent at least 19 mEHT treatment sessions. All pancreatic cancer diagnosis was confirmed during routine diagnostic protocol by histological examination between 2014.12.26 and 2019.10.17. Data collection was closed on 2020.01.31. The time elapsed between the date of diagnosis and death was as overall survival (OS).

Results: In first step each case-patient was individually matched to a control-patient by age, sex and chemotherapy administration during mEHT treatment. To reach higher similarity in overall status of the case and control patients also presence or absence of distal metastases and emerging ascites were taken in count as matching criteria by generating case-control pairs.
Of note, a trend in difference was found in overall survival of patients in case-control pairs matched for age, sex and chemotherapy receiving during mEHT treatment favoring mEHT ($p=0.0704$). Overall survival of inoperable pancreatic cancer patients with or without distant metastasis in both case and control groups was analyzed, metastatic disease resulting in significantly higher OS ($p=0.022$). Overall survival with or without the presence of ascites in both case and control showed a trend favoring mEHT treatment as well ($p=0.0611$). Elapsed time between diagnosis and start of mEHT treatment did not significantly influence overall survival.

Discussion: In our series of inoperable pancreatic cancer patients treated with mEHT applied as concomitant therapy, we have detected a significant improvement in overall survival, especially in metastatic setting. To further analyze the biological background for this treatment response, we have concluded analyses investigating the tumor-host immunological interface and quality of life, and we have developed the protocol for a randomized clinical trial for this patient group.

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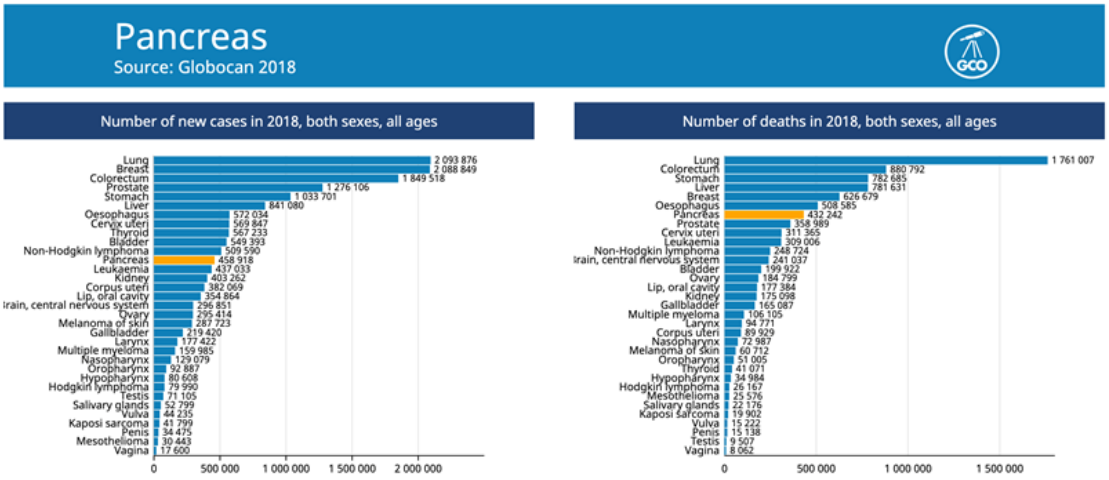
Cancer Center,

Department of Internal Medicine and Oncology

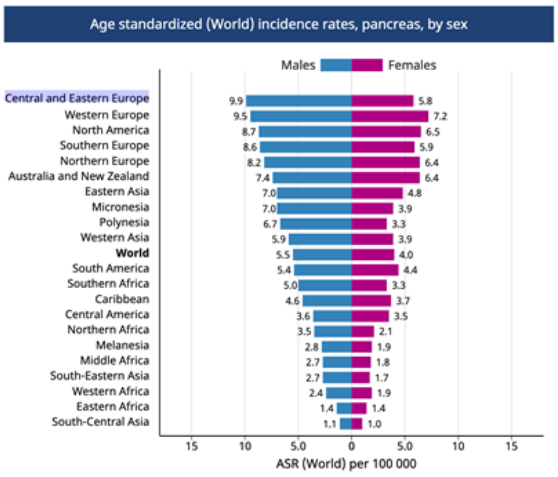
38th Conference of International Clinical Hyperthermia Society

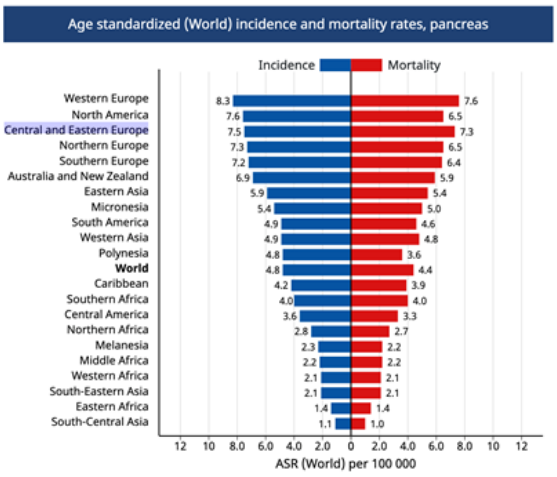
5th November 2020

New cases and deaths worldwide

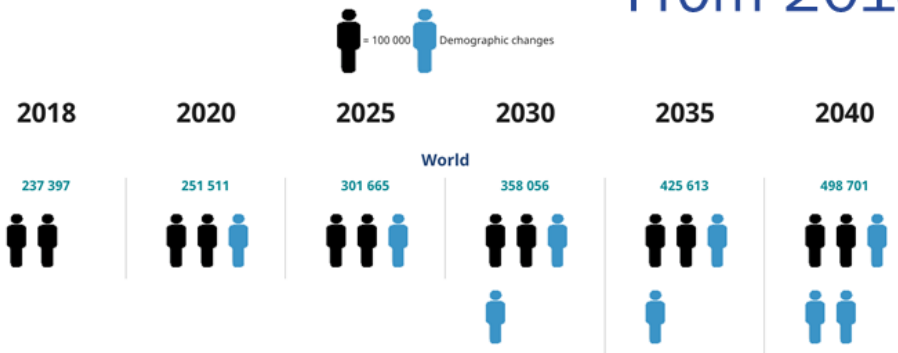


Incidence and mortality regionally





From 2018 to 2040



		2018	2040			
		Number	Number	Demographic change	Change in risk	Overall change
World	Males (APC 0%)	243 033	426 284	183 251 (+75.4%)	0	183 251 (+75.4%)
World	Females (APC 0%)	215 885	388 992	173 107 (+80.2%)	0	173 107 (+80.2%)
World	Both sexes	458 918	815 276	356 358 (+77.7%)	0	356 358 (+77.7%)

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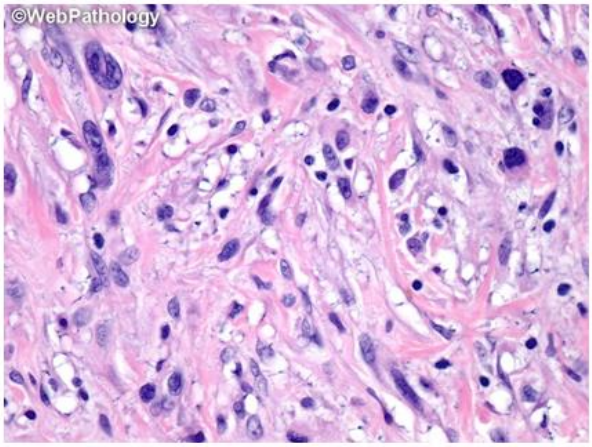
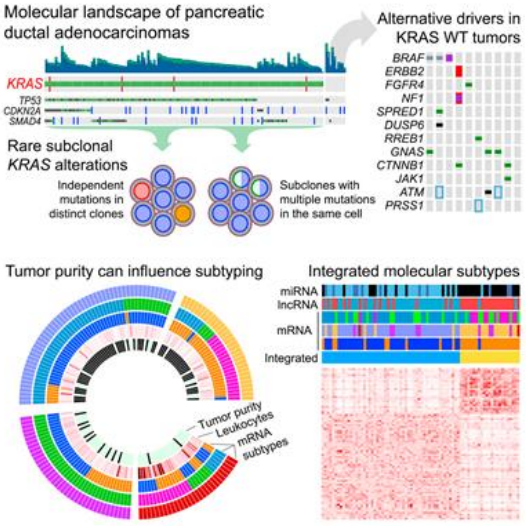
Morphology and underlying genetics

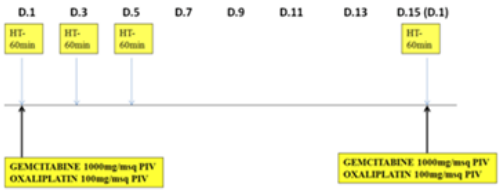




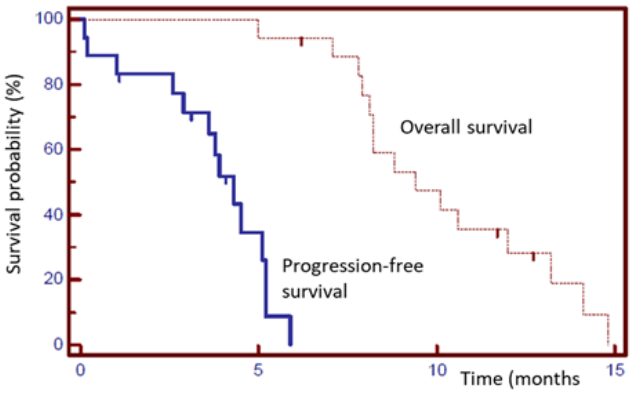
Pancreatic studies

Metastatic Pancreas; Phase II study (n=26)

Second-line chemotherapy in combination with Oncothermia for patients with refractory metastatic (progressive in liver) pancreatic cancer.
The treatment protocol was intravenous chemotherapy (gemcitabine, 1000 mg/m2 IV and oxaliplatin 100 mg/m2 [GEMOX]) on day one combined with mEHT (days1, 3 and 5); and the protocol repeated by every two weeks.



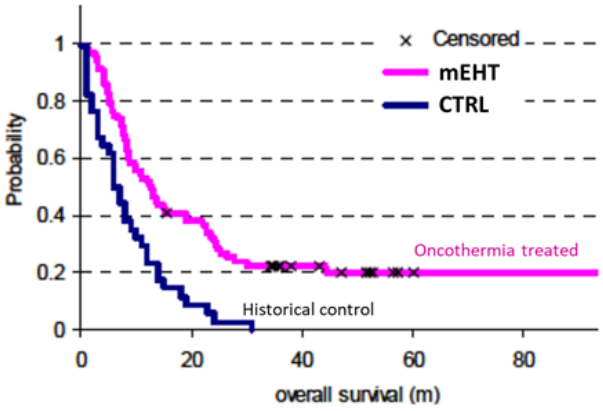
Volovat et al.; (2014); *Romanian Reports in Physics, 66:166–174*



Pancreatic studies

Phase II study of advanced, metastatic pancreas cancer (n=99) Dani A, et al. (2008) Forum Hyperthermie 1:13–20

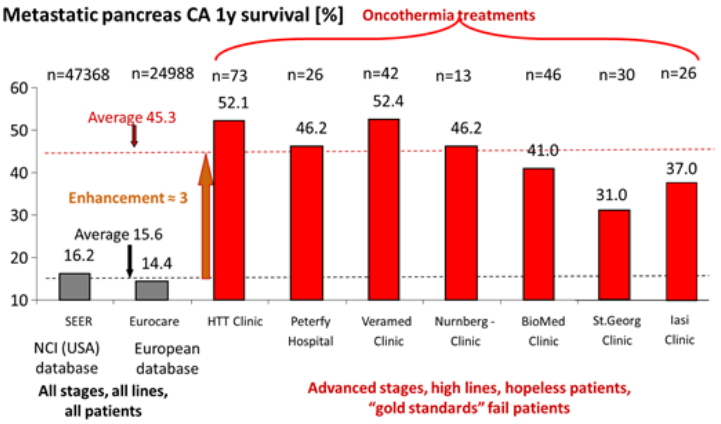
Phase II clinical trial, double center (A & B), single-arm in comparison to historical control from the same hospital, same doctors. 40+% of patients had multiple metastases. The trial includes a cohort of heavily pretreated patients (3+ lines), and due to the refractory or another fail of the conventional therapies oncothermia was applied as monotherapy. The first and subsequent year survivals were: 1st:50.5%, 2nd: 27.3%, 3rd:15.2%, 4th:8.1%, 5th:3%. These values are significantly higher than the values from the large databases (SEER and Eurocare).



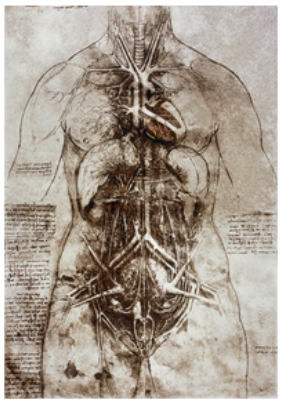
Pancreatic studies

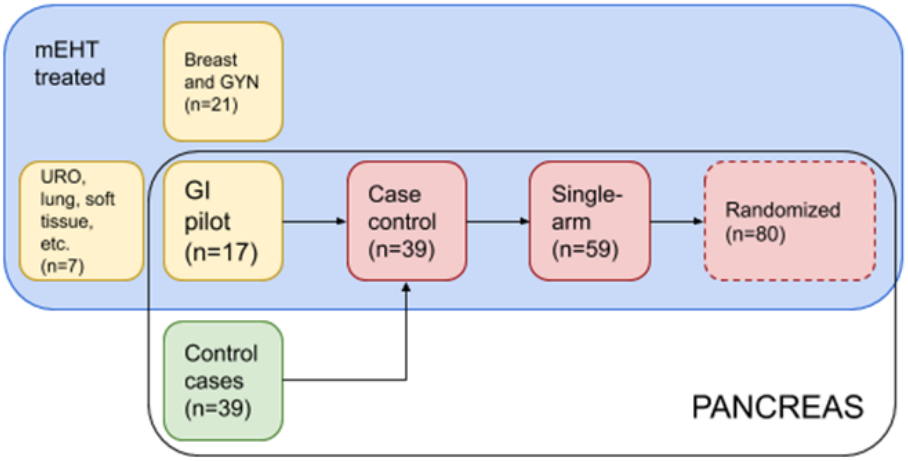
1st year survival comparison of pancreas studies in different hospitals using oncothermia protocol

The achieved results of 1st year survival is compared to the same time achieved results in USA and EU, according to the relevant databases; SEER and EuroCare. The weighted average is nearly 3 times higher for oncothermia treated patients than the general expectation. This result is despite the fact, that the general statistics contain all the patients, while patients treated with oncothermia are all in high-line treatment advance stages, where the "gold standards" fail.



mEHT studies at Semmelweis Cancer Center





Study Design and Patient Selection

- retrospective single-center case-control study
- 78 pancreatic cancer patients (ductal adenocarcinoma)
- all pancreatic cancer diagnosis was set during routine diagnostic protocol by histological examination between 2014.12.26 and 2019.10.17.
- case group comprised of 39 inoperable pancreatic cancer patients
- data collection was closed on 2020.01.31.
- each case-patient was individually matched to a control-patient by age (±5 years), sex and chemotherapy received during mEHT treatment.
- presence or absence of distal metastases and emerging ascites. (However, this led to the exclusion of some case-patient as no suitable control was found.)

Treatment

- first mEHT treatment at Semmelweis University Cancer Center between 2016 September and 2019 November
- Instruments: mEHY-2000, mEHY-2030
- at least 19 mEHT treatment sessions

median number of mEHT sessions (range)	49 (19-154)
elapsed time from diagnosis to mEHT treatment (days from pathological diagnosis)	41 (0-717)

- Power from 50W to 100W, then 100W to 150W in an hour session
- (2 or 3 times per week, as long as tolerated)
- systemic treatment: FOLFIRINOX and gemcitabine-based protocols (± platinum / 5FU)

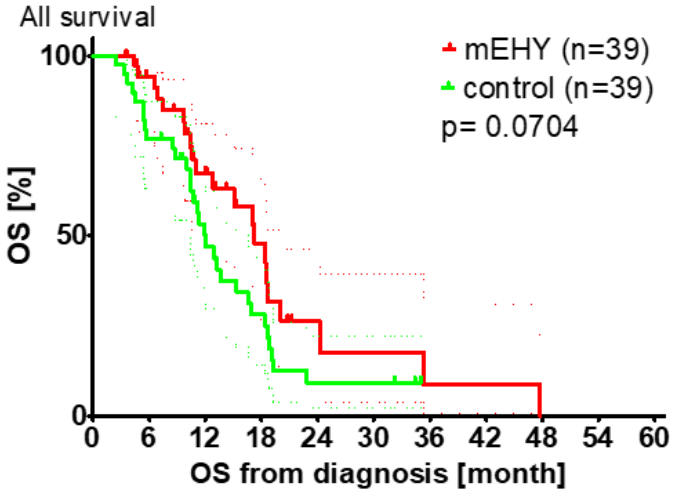
Statistical analysis

- The time elapsed between the date of diagnosis and death from any cause was as overall survival (OS).
- Follow-up of the patients were closed at 2020.01.31. Patients alive at this time point were censored.
- Survival rates were estimated using Kaplan-Meier analysis supported by log-rank tests, and comparison of other parameters between case and control group were investigated using t-test or Fisher exact test for continuous and categorical variables.
- Two-sided p values < 0.05 were considered as significant.

Basic demographic and clinical characteristics

		mEHT treated	Control	p=	
median age (range)		66 (45-84)	68 (45-77)	0.8801	t-test
male gender		18 (46.1)	18 (46.1)	matched	
chemotherapy	GEM/B	24 (61.5)	24 (61.5)	matched	
	Folfirinox	8 (20.5)	8 (20.5)	matched	
	GEM+CDDP	5 (12.8)	5 (12.8)	matched	
	GEM+5FU+LV	1 (2.6)	1 (2.6)	matched	
	Gem+oxaliplatine	1 (2.6)	1 (2.6)	matched	
without pathological ascites		23 (58.9)	21 (53.8)	1.000	Fisher exact test
without distatnt metastasis		16 (41.0)	12 (30.7)	0.3585	Fisher exact test
not-operable		39	39	matched; enrollment criteria	
median overall survival [month]		10.77 (3.5-47.7)	10.83 (2.5-35.0)	0.9059	t-test
1 year survival		18 (46.2)	16 (41.0)	0.6566	Fisher exact test
2 year survival		3 (6.8)	3 (6.8)	1.000	Fisher exact test
3 year survuval		1 (2.6)	0 (0.0)	1.000	Fisher exact test

trend in difference was found in overall survival in case-control pairs (matched for age, sex and chemotherapy receiving during mEHT treatment)



Dotted line represents asymmetrical 95% confidence interval calculated in the Kaplan-Meier analysis

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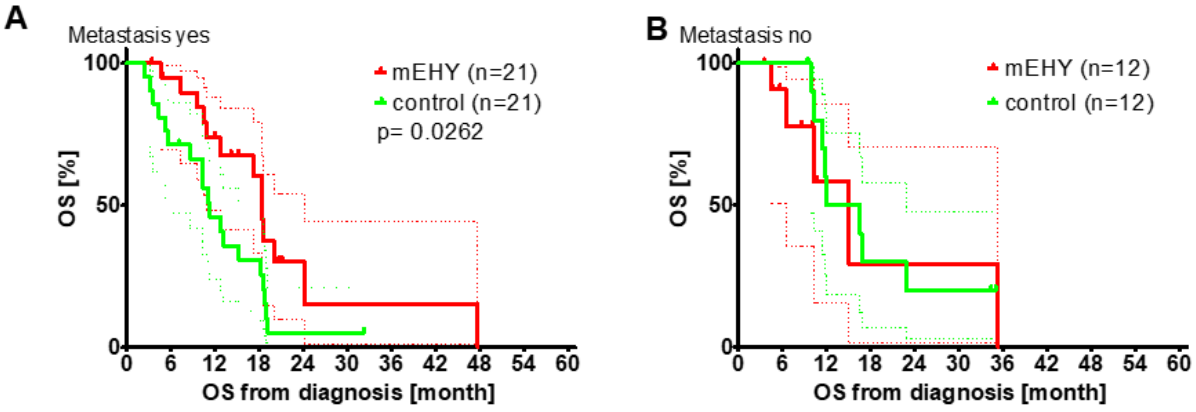
emerging **distant metastasis** or ascites in the patients' history was used as additional matching criteria by making case-control pairs



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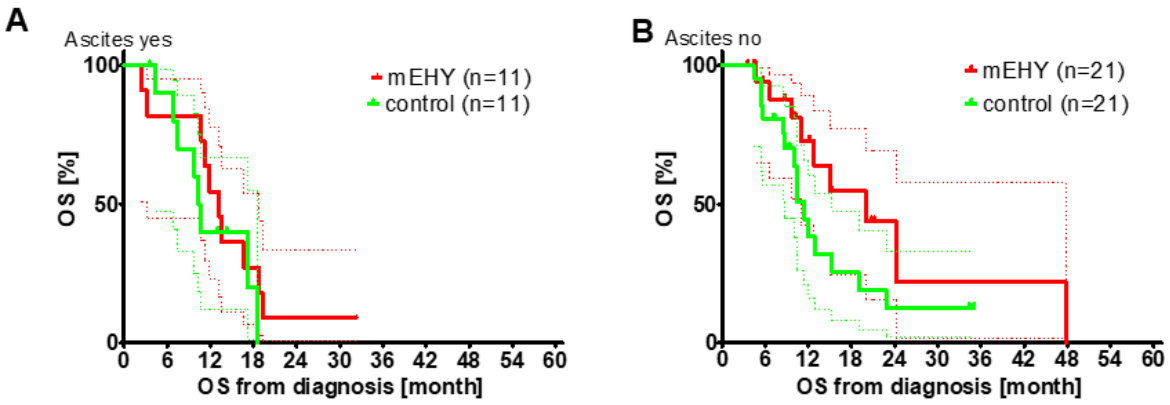
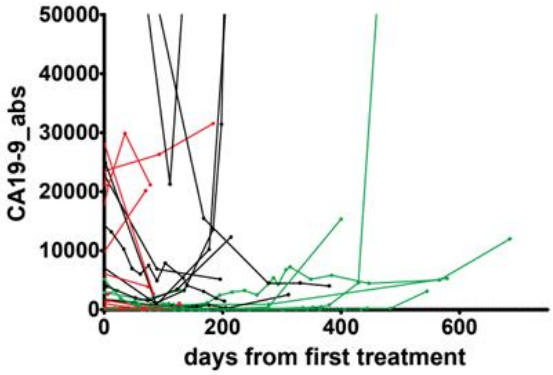
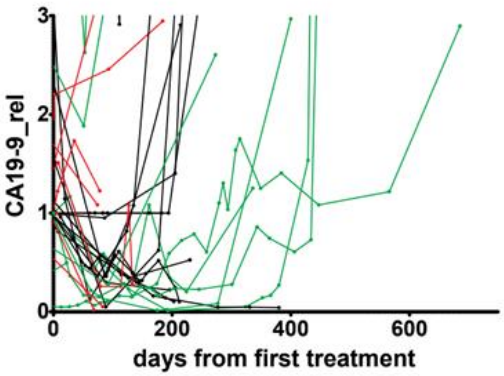
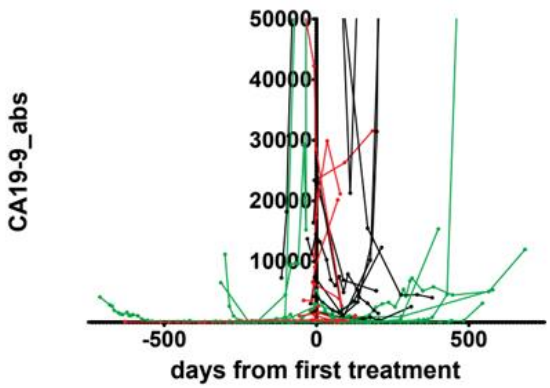


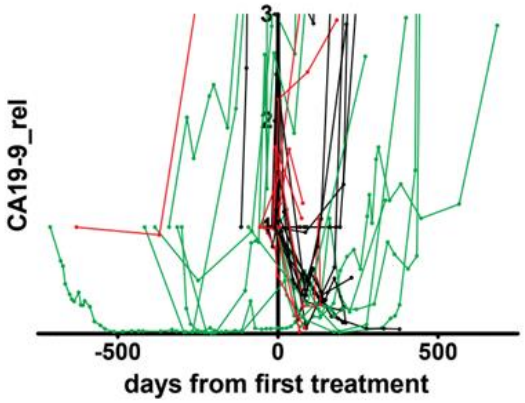
Tumor markers – CA19-9



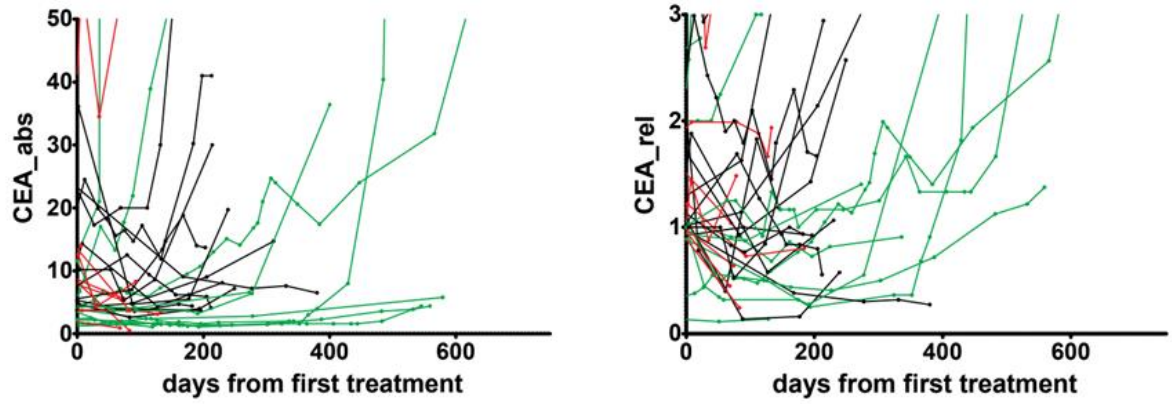


Predicting response with CA19-9

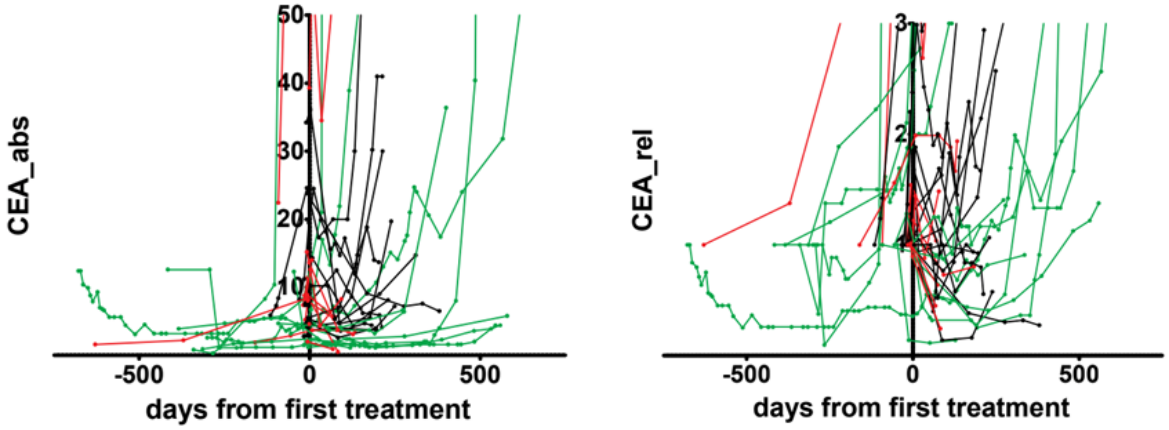


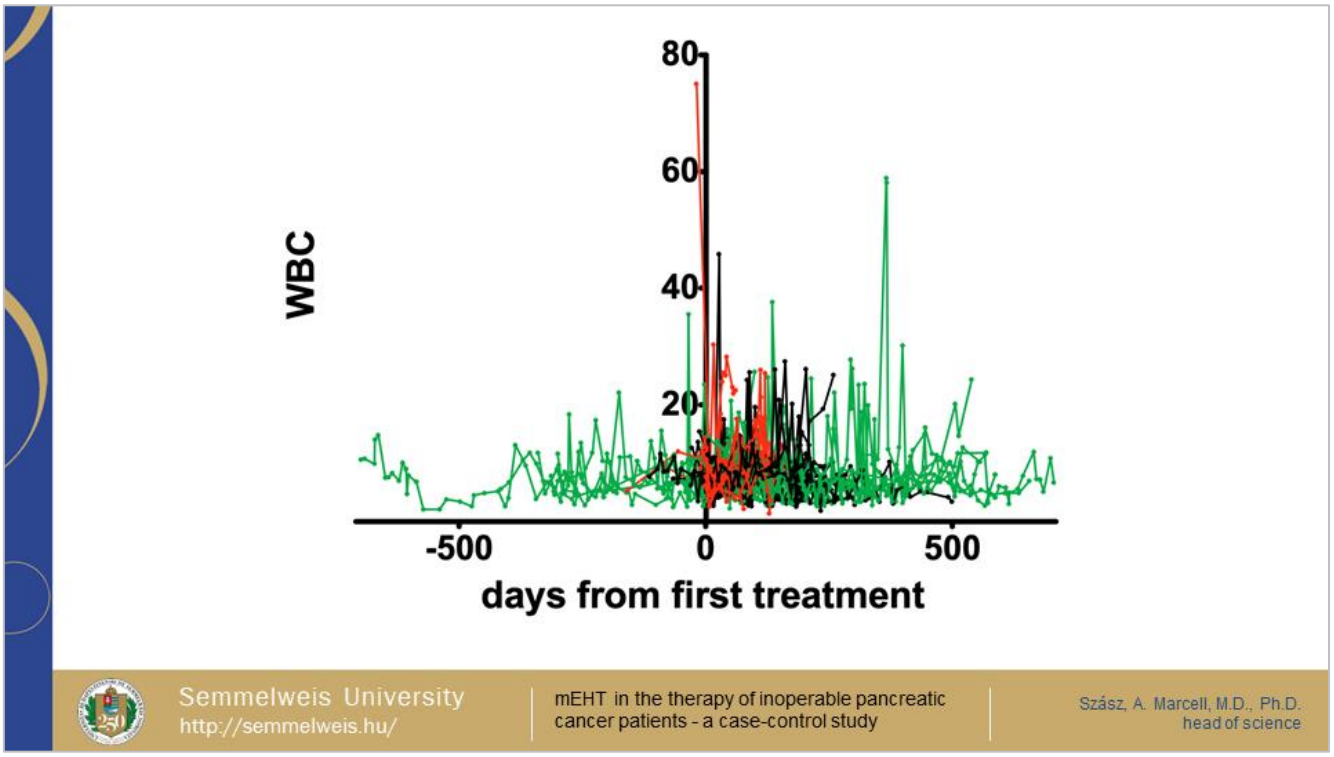


Tumor markers - CEA

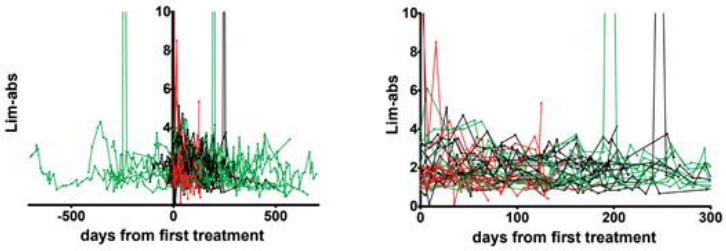


Predicting response with CEA

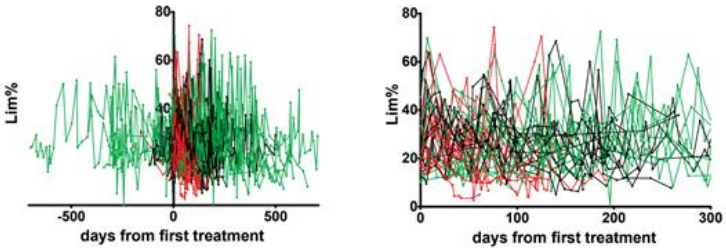




Lymphocyte counts



Intra-patient variation



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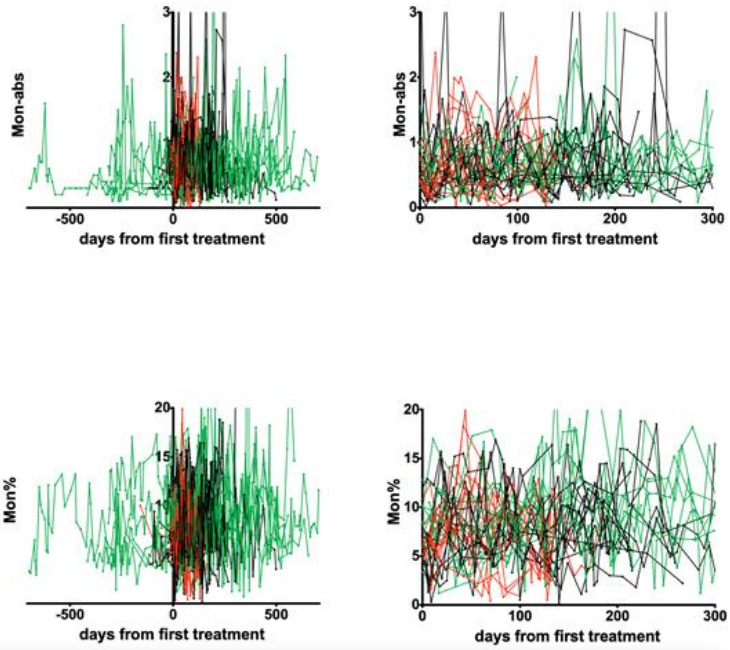
Monocytes



Conclusion

- Modulated electro-hyperthermia is improving overall survival in inoperable pancreastic cancer, especially in the metastatic setting
- Mechanism and prediction of response has to elaborated further
- Randomized clinical trial in metastatic pancreatic cancer to be performed
- AI based evaluation under progress

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