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Deep Hyperthermia with Radiofrequencies in Patients with Liver Metastases from Colorectal Cancer

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Abstract. *Patients at advanced stage of colorectal cancer with liver metastases have been treated with deep hyperthermia alone or in combination with chemotherapy (5-FU + FA+MMC). Hyperthermia was achieved by arrangements of capacitive electrodes with a radiofrequency field of 13.56 MHz (RF-DHT). This prospective open single-arm clinical study with 80 patients suffering from liver metastases from colorectal cancer gives some first hints, that deep RF-hyperthermia alone may have a substantial beneficial effect on overall survival time of patients with liver metastases from colorectal cancer. Long lasting no-change, partial and even some complete remissions could be observed. The overall median survival time from progression of metastases or relapse was 24.5 months and survival rates at 1, 2 or 3 years from first diagnosis of metastases or progression were twice as high as expected from patients treated with chemotherapy. The combination of hyperthermia with delayed chemotherapy did not change overall survival time. These encouraging results deserve to be confirmed in randomized clinical studies.*

Malignant tumors of the colon and rectum represent the second leading cause of cancer deaths in Western societies. 21 (colon) and 29 (rectum) % of these patients are diagnosed at an incurable stage mostly with distant metastases. Depending on tumor stage 20-50 % of these patients develop metastases or recurrences after potentially curative surgery and adjuvant chemotherapy, mostly within 2 years, and only 10-15 % of these tumors are resectable. The prognosis for advanced stages of colorectal cancer is still very poor, especially for unresectable tumors.

The treatment of patients with hepatic metastases from colorectal cancer is still controversial. While some patients undergo systemic chemotherapy from time of diagnosis with very limited results, other patients are not treated with cytostatics or only with the beginning of a symptomatic stage of disease.

Fluoropyrimidines (f.e. 5-fluorouracil/S-FU) and irinotecan remain the most effective single chemotherapeutic agents for patients with colorectal cancer. According to a meta-analysis, 5-FU + folinic acid yielded 23 % objective responses, and an approximate 12-month median survival (range 6-15 months) in previously untreated patients with metastatic colorectal cancer (1). Hepatic artery infusion (HAI) with FUDR for patients with liver metastases does not substantially improve survival and allows overall survival of 10-17 months.Toxicity of HAI-treatment can be significant and include chemical hepatitis, biliary sclerosis, catheter thrombosis, and duodenal ulceration and hemorrhage. Overall, 5-FU does not demonstrably effect survival for patients with stages Dukes A, B, and D and especially relapsed patients (for review see 2, 3). The dose limiting toxic side effects are besides those of nausea, vomiting and alopecia, above all leucopenia, mucositis, pharyngitis and oesophagitis, dermatitis, palmar-plantar erythrodysesthesia, enteritis and diarrhoea, which can be life-threatening. Patients who fail to respond to an initial 5-FU therapy seldom respond to 5-FU administered on a different dose or schedule or with a different modulating agent. New cytostatics, irinotecan (CPT-11) and oxaliplatin, show substantial toxicity without significant improvement of survival time (4, 5). Expected survival rates of patients with multiple metastases of colorectal cancer are 40 % (range 39 - 56 %) at 1 year, 15 % at 2 years and 1 % at 3 years, respectively (6, 7).

The effects and scientific evidence of hyperthermia are thermosensitivity of tumor tissue, especially at decreased pH and pO2, immunological effects and apoptosis induced by heat (see Table I). Immunological and biological effects due to heat are accelerated emigration and migration of peripheral blood mononuclear cells, activation of effector cells, induction and secretion of cytokines, expression of heat shock proteins (HSP) which increase the antigenicity of cancer cells (Table II). Direct interactions between electromagnetic waves in the frequency range of 8-15 MHz

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Table I. *Effects and rationale of deep RF-hyperthermia.*

- Thermosensitivity of tumor tissue (> 42°)
- Synergistic effects between heat and cytostatic agents
- Increased thermosensitivity at decreased pH and pO_2
- Immunological effects and induction of apoptosis
- Interactions of cell particles with electromagnetic waves

Table II. *Immunological and biological effects of heat.*

- Emigration of PMNC
- Activation of effector cells
- Induction of cytokine synthesis/secretion (IL-1/-2, TNF)
- Expression of "heat-shock proteins" (HSP)
- Increased antigenicity of cancer cells (HSP:TAA)
- Induction of apoptosis

Table III. *Study design and eligibility criteria.*

Study design:

- Prospective, open, single-arm phase II-study

Inclusion criteria:

- Liver metastases from colorectal cancer (histologically proven)
- Unresectable hepatic lesions
- Age 20 to 80 years
- Performance Status WHO/ECOG <4
- Informed consent

Exclusion criteria:

- Simultaneous chemo-/radiotherapy at study entry
- Life expectancy < 4 weeks
- Pregnancy, no consent

Table IV. *Technical and therapeutic features.*

Frequency:	short waves 13.56 MHz
Electrodes:	capacitive
Temperature:	42 - 43°C (calc.)
Cooling:	cutaneous 15°C
Therapy intervals:	1h/biweekly 8 times per cycle

and the membrane of cancer cells, may be a further explanation for cytostatic or cytotoxic effects of RF-Hyperthermia.

Materials, Methods and Statistics

After observing partial and even complete remissions of liver metastases and primary liver tumors by RF-DHT and in search of less toxic treatments we started, in April 1993, an open prospective single-arm study by treating 80 patients with progressive liver metastases from colorectal cancer with deep hyperthermia with radiofrequencies of 13.56 MHz (RF-DHT). Inclusion and exclusion criteria are listed in Table III. A central exclusion criterium was a simultaneous chemotherapy at beginning of hyperthermia but the patients could have been pretreated with chemotherapy.

The short waves of 13.56 MHz were applied by capacitive electrode technique with cooling of the skin surface with 15°C (Theratherm®, Vigevano, Italy; Oncotherm® 2000, Bad Aibling, Germany). The applied RF-power ranged between 70 and 130 watts and the calculated average temperature of the tumors was between 42 and 43°C. For ethical reasons invasive measurements of the temperatures at different tumor sides was disapproved. Each RF-DHT treatment interval took biweekly 1 hour. 8 treatments per course were performed (Table IV). The courses were repeated after 5 to 6 weeks till progression of the tumors. 30 of the 80 patients treated initially only with RF-DHT received a palliative chemotherapy during the follow-up time. In these cases the median time between first hyperthermia and onset of palliative chemotherapy was 4.5 months. In addition, the patient received unspecific immunotherapy with thymus peptides and plant-lectines (1 ng/kg ML-I) and proteolytic enzymes.

Patient characteristics are listed in Table V. All 80 patients with a median age of 60, showed liver metastases and 36.5 % extrahepatic metastases: 10 % lung metastases, 12.5 % distant lymph node metastases, 9 % peritoneal carcinosis, 4 % bone metastases, and 1% metastases at other sides.

By time of admission into the hospital most of the patients have been already reached a far advanced stage of disease. The relevant prognostic factors are listed in Tables V and VI: 69 % of the patients were pretreated with chemotherapy, which failed and the tumor progressed before admission into the hospital for hyperthermia treatment. 56 % of the patients showed multiple liver metastases, in the other cases the tumors were not resectable. 39 % of the metastases were synchronous and 61 % developed metachronous. Lactic acid dehydrogenase (LAH) was increased in 40 % of the cases and alkaline phosphatase in 49 %. The performance status was ≥ 1(WHO/ECOG-Score) in 63 % of the patients.

The accrual time was 52 months from 4/93 - 8/97 and the follow-up time 23 months from beginning of RF-DHT. The median time between first diagnosis of liver metastases and start of RF-DHT was 7.4 months, ranging between 14 and 2200 days. The median time between first diagnosis of cancer and diagnosis of metastases or relapse was 4 months (range 30 - 1740 days). The follow-up rate was 96.3 % (Table VII).

Table V. *Patient's characteristics.*

Number of patients	n = 80	
Median age (yrs) (Range)	60 (31- 82)	
Performance status (WHO/ECOG)	0 = 37 %	
	I = 32 %	
	II = 23 %	
	III = 8 %	
Sites of metastases	*n*	*%*
Liver	80	100
Lung	8	10
Lymph nodes (cN+dinstant)	10	12,5
Peritoneal carcinomatosis	7	9
Bone	3	4
Others	1	1
Histology	Adenocarcinoma	n = 80
Prior chemotherapy	*n*	*%*
5-FU + Leucovorine	52	65
HAI*)	2	2,5
Others	1	1,3
Prior liver resection	13	16

*) HAI: Hepatic Arterial Infusion

Table VI. *Prognostic factors.*

Synchronous metastases:	39 % (n = 32 pts.)	
Metachronous metastases:	61 % (n = 48 pts)	
Multiple liver metastases:	56 % (n = 45 pts)	
Lactic acid dehydrogenase (LAH):	40 % > 240 U/l	
Alkaline phosphatase (SAP):	49 % > 170U/l	
Tumor marker:		
CA 19-9	> 24 U/l	65 %
CEA	> 2.5 ng/l	84 %

Table VII. *Follow-up.*

• Accrual time	4.3 yrs
• Follow-up time	23 months from begin of RF-DHT
• Follow-up rate	96.3 %
• Median time between 1st dx of liver metastases and beginning of RF-DHT	7.4 months [range 14 -2200 days]
• Median time between 1st dx and dx of metastases	4 months [range 30 - 1740 days]
• Median time between begin of RF-DHT and palliative CHT (n = 30 pts.)	4.5 months [range 53-691 days]

The primary endpoints of the study were median overall survival time and survival rates as an intention-to-treat-analysis. Secondary endpoints were clinical benefit (Quality of life questionaire EORTC QLQ C-30) and the course of the tumor markers CEA and CA 19-9. During the follow-up time all the different chemotherapies introduced into treatment of colorectal cancer did not alter survival time of patients with metastasized colorectal cancer significantly, so historical control groups with liver metastases can be used for comparison of survival.

Results

Median total survival time of all 80 patients from first diagnosis of disease was 34.4 months, from first diagnosis of progression (metastases or relapse) 24.5 months, and from beginning of first RF-deep hyperthermia alone (n = 50) 16 months (Table VIII). Patients who received RF-DHT followed by chemotherapy in combination with hyperthermia (n = 30) survived for a median of 11 months. The Kaplan-Meier survival curves are shown in Figure 1; patients alive at time of analysis have been censored.

Survival rates of all patients (n = 80) from first diagnosis of progression (metastases or relapse) are 91 ± 3 %, 51 ± 6% and 31 ± 6 % at 1, 2 and 3 years, respectively. From onset of first RF-DHT alone the survival rates were 61 ± 8%, 13 ± 7% and 5 ± 4%, respectively (n = 50 pts.). 30 patients received chemotherapy after initial RF-DHT alone with 1- and 2-year survival rates of 49 ± 10% and 16 ± 7%, respectively (Table IX).

The expected survival of patients with metastasized colon cancer after 2-years would be expected according to historical control groups between 24 and 36 %. On the assumption of a statistical power of 90 % (type II error of

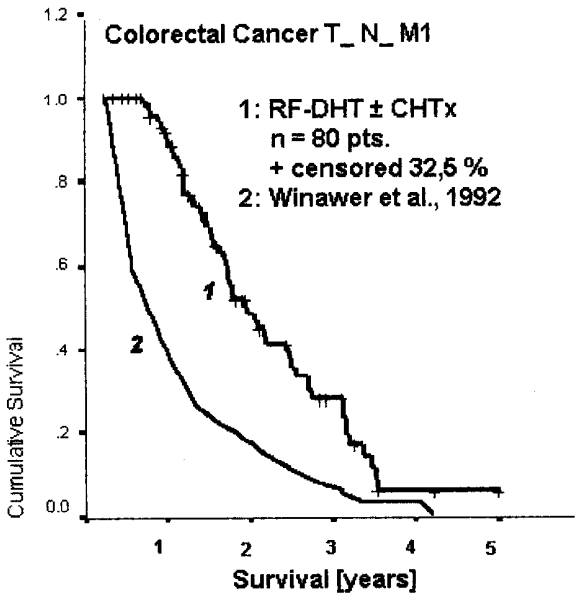

Figure 1. *Kaplan-Meier Survival Curves of all 80 patients compared to historical control group.*

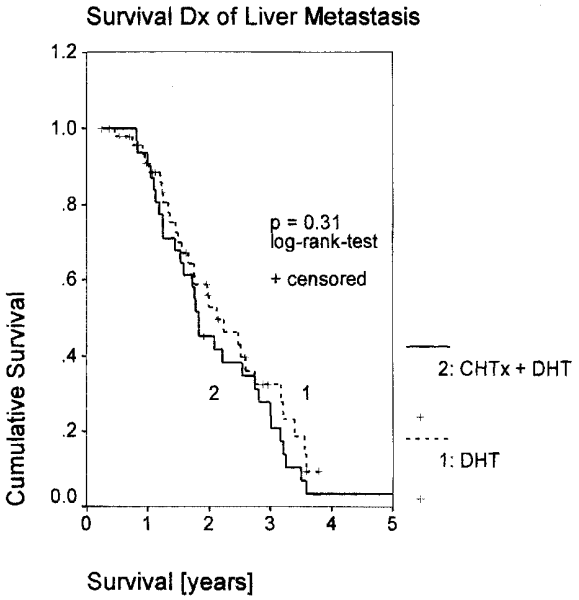

Figure 2. *Kaplan-Meier Survival Curves comparing patients treated with hyperthermia alone (n=50) and combined chemotherapy with 5-FU+FA+MMC plus hyperthermia (n=30).*

10 %), an expected standard deviation of 6 % and a sample size of 80 patients an increase of more than 9 patients surviving would be statistically significant on a significance level of α = 1 % (Table X). In this study with 51 % patients surviving after 2 years, 12 patients survived more than to be expected compared to best reported survival rates in the literature of 36 % (Table X).

The change of tumor marker responses after the first hyperthermia cycle, measured at the start of the 2nd cycle, is listed in Table XI. In 9 % of the patients the tumor marker CA 19-9 decreased the more than 50 %. In 15 % and 28 % of the patients the tumor markers CA 19-9 and CEA decreased between 25 and 50 % after the first hyperthermia cycle. Overall biochemical responses were seen in 25 % of the patients (tumor marker CEA and CA 19-9).

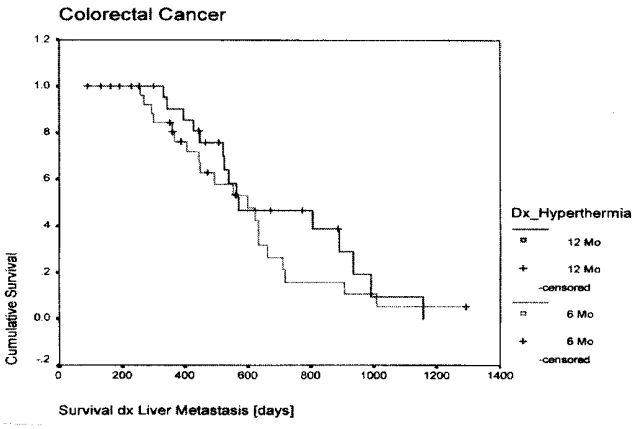

Figure 3. *Kaplan-Meier Survival Curves after stratification according to time interval between first diagnosis of progression and onset of hyperthermia.*

Discussion

This prospective single-arm open study gives some first hints that treatment with deep hyperthermia with radiofrequencies alone will have a substantial beneficial influence on overall survival of cancer patients with liver metastases from colorectal carcinoma. Long lasting no change, partial remissions and some complete remissions have been observed. The observed median overall survival time from first diagnosis of liver metastases of 24.1 months is significantly longer than expected from conventional treatments with chemotherapy (8 - 11 months) and the 1-, 2- and 3-year survival rates of patients treated with RF-DHT alone was from progression of disease about twice time higher. Though most of the patients were at an advanced stage of the disease, at a median time of 7.4 months after 1st diagnosis of disease, and 69 % of the patients had already had palliative chemotherapy, the 1-

Table VIII. *Median total survival time.*

			months
•	From 1st Dx of metastases:		
	DHT alone	(n =50)	24,4
	DHT + CHT	(n = 30)	21,5
	All patients	(n =80)	24,1
	Expected		8-11
•	From 1. DHT- treatment:		
	DHT alone	(n = 50)	16,1
	DHT + CHT	(n = 30)	11,3
	All Patients	(n = 80)	14,5
•	From combined DHT + chemotherapy		
	All Patients	(n = 30)	6,1
•	From 1st diagnosis of carcinoma		
	All Patients	(n =80)	34,0

Table XI. *Tumor marker-response after the 1st hyperthermia cycle.*

Response	CA 19-9 (n = 54)	CEA (n = 57)
PR(decrease ≥ 50 %)	9 %	0 %
NC (decrease < 50 % increase ≤ 25 %)	16%	28%
PD (increase > 25 %)	75%	72 %

Table IX. *Survival rates.*

	1-Year survival	2-Year survival	3-Year survival	4-Year survival
From 1st dx of metastasis	%	%	%	%
DHT alone (n = 50)	92 ± 4	51 ± 8	30 ± 8	n.d.
DHT±CHT(n=30)*	go ± 5	49±9	32±9	8±7
All (n =80)	91±3	51±6	31±6	n.d.
Expected **	48 - 58	24 - 36	14 - 19	7
From 1st RF-DH	%	%	%	%
DHT alone (n = 50)	61 ± 8	13 ± 7	5 ± 4	n.d.
DHT ± CHT (n = 30)*	49 ± 10	16 ± 7	n.d.	n.d.
All (n = 80)	56 ± 6	15 ± 5	5 ± 4	n.d.
From beginning of palliative CT				
All (n = 30)*	16 ± 8	11 ± 7	n.d.	n.d.

Table X. *Statistical analysis.*

The following estimates were based on the critical test for single proportions, with two-tailed alpha = .01, Statistical Power = 90
Primary Hypothesis: Survival after 2 Years

Cancer	N	Expected survival after 2 yrs. (H_0)		Minimum detectable increase in survival		Observed no. of pts. surviving
	Pts.	Rate (%)	N_e	Rate(%)	N_A	N_0
Colon-Ca.	80	36	29	+ 11	>38	41 (=51%)

year survival rate from the beginning of the first RF- DHT was 61 ± 8 % compared to the expected 48 - 58 % in historical control groups from first time of diagnosis of metastases.

The application of chronomodulated chemotherapy during the follow-up time in combination with hyperthermia did not significantly change survival time. From this data it may be concluded, that hyperthermia by itself could substantially prolong survival time of cancer patients with liver metastases from colorectal cancer.

Prognostic factors of the treated group were poor in comparison to historical control groups, due to the late stage of disease. Lactic acid dehydrogenase, an essential prognostic factor, was elevated in 40 % of the patients and alkaline phosphatase in 49 %; 39 % of the patients showed synchronous metastases. The tumor marker CEA was elevated in 84 % of the patients and CA 19-9 in 65 %, these decreased in 25 % of the patients after the 1st hyperthermia cycle by more than 25 %, and in 9 % by more than 50 %. A relationship between CEA and CA 19-9 respectively and clinical stage and survival has been repeatedly demonstrated (8, 9). Decrease in tumor volume could also be demonstrated by ultasound and CT-scan technique. The delay in treatment with hyperthermia may be a cause of patient selection. Therefore we analysed survival depending from the time between first diagnosis of metastases and begin of hyperthermia treatment. Figure 3 shows, that no difference in survival time between a subpopulation of

patients stratified according to the time between first diagnosis of progression and onset of hyperthermia (6 months compared to 12 months) could be observed. No significant difference between survival of patients treated with hyperthermia alone and chemotherapy plus hyperthermia could be observed (Figure 2).

First correlation of the applied power of the electromagnetic field with the survival data did not show strong functional dependency at higher fields. Therefore it is likely not heat alone, but also electromagnetic interactions between the EM-field and the dielectricity of the cell membranes that may be at least part of the cytotoxic or cytostatic effect. These encouraging results deserve to be confirmed by randomised clinical studies.

Acknowledgements

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