

**Lower and less toxic doses of chemotherapy by combining it with hyperthermia and complementary treatments**

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## **Lower and less toxic doses of chemotherapy by combining it with hyperthermia and complementary treatments.**

### **Introduction:**

Hyperthermia is an important tool to improve the efficacy of chemotherapy and radiation in cancer. Numerous studies have been published about hyperthermia treatment in cell cultures, in animal experiments but also in patients. These studies include randomized studies, phase 2 studies but also many successful case reports providing evidence for the benefit of hyperthermia.

In neoadjuvant treatment the goal would be a higher remission rate and faster and more complete shrinkage of the tumors so that surgery would be easier.

In curative treatment the goal would be to achieve a higher rate of cure.

In palliative treatment, however, the focus would be not so much on high remission rates as a remission itself is not as important as the overall survival time. Achieving a higher remission rate with very toxic chemotherapy even may result in shorter survival time (and reduced quality of life in the remaining time).

As hyperthermia increases the efficacy of chemotherapy and radiation we have to consider in the palliative setting a dose reduction of chemotherapy when given together with hyperthermia. By controlling a malignant disease with less toxic treatments not only quality of life would be preserved, also survival time may be prolonged as patients would suffer from less toxicity.

### **Methods:**

Hyperthermia means heating up cancer tissue up to 42°C (107.6°F). In several experiments it has been shown that chemotherapy works more efficient if the temperature of cancer tissue is increased. There can be a linear or even an exponential increase of the activity of cytostatic drugs.

Hyperthermia for healthy tissues is not dangerous but in cancer cells hyperthermia already alone may have a damaging effect. This includes disturbances of the regulation of cell membranes, denaturation of p-glycoproteins (which are responsible for resistances of tumor cells against chemotherapy or radiation), increased blood flow into tumor tissues and also possibly getting cells out of a dormant status.

There are different types of hyperthermia:

Local hyperthermia includes superficial hyperthermia with infrared radiation or microwaves and deep regional hyperthermia using short wave irradiation. Depending on the devices and technical features energies up to 600 W and more may be used.

(We use the Oncotherm device with 13.56 MHz and energies up to 150 Watts).

Local hyperthermia treatment takes 1 hour for each session. The treatment can be repeated frequently (the gap between 2 treatments should be at least 48 hours to avoid thermal tolerance). Chemotherapy is given simultaneously to a local hyperthermia session.

The efficacy of hyperthermia even can be increased if a tumor is treated with chemo-embolization. By this procedure tumors are less perfused which allows higher accumulation of heat tumor as the cooling effect of the bloodstream is reduced.

In whole body hyperthermia the body core temperature is heated up 41.5°C (106.7° F). This is only possible in analgo-sedation and intensive care monitoring. The temperature of the body is increased by whole body water filtered infrared-irradiation using energies up to 2000 Watts. This radiation heats up the small blood vessels under the skin and in this way the blood gradually heats up the body core until the desired level is reached. Chemotherapy is given at the peak temperature of whole body hyperthermia (Image 1). The chemotherapy protocols for hyperthermia depend on the different diseases. But the chemotherapy can be modified in a way that lower and less toxic doses may be given if combined with hyperthermia.

### **Results for a selection of different cancers:**

#### **ENT-Cancers:**

Advanced ENT -cancers are difficult to treat by surgery as often tumors are surrounded by vulnerable structures in face, throat, skull base and neck. Standard chemotherapy in this condition would be a rather toxic program of 5 days Cisplatin together with 5-FU as continuous infusion. Together with hyperthermia a 4 day program would be sufficient. (Image 2)

Together with local hyperthermia this treatment is efficient even in large tumors. (Image 3).

#### **Lung cancer:**

In patients with non-small cell lung cancer whole body hyperthermia and local hyperthermia together with chemotherapy can be highly efficient.

The dose regime would follow a platin based chemotherapy, but the doses of Carboplatin and Gemcitabine or Vinorelbine could be reduced about 20%.

Not only the primary tumors in the lung often respond quite well, also in metastatic disease fast changes can be noticed resulting in reduction of symptoms. (Image 4).

#### **Colorectal cancer:**

The chemotherapy protocols in colorectal cancer are mainly the FOLFOX and the Folfiri protocol, which can be combined with the antibodies Bevacizumab or Cetuximab. Together with hyperthermia the oxaliplatin dose would be kept at the standard level. Irinotecan could be reduced and also 5-FU significantly could be reduced if given as chronomodulated treatment overnight with 50% of the total dose between 2 a.m. and 6 a.m. Also, Capecitabine may be used together with hyperthermia in a reduced dose (Image 5).

Even patients with a high tumor load and predicted short survival time in which a standard chemotherapy is not possible any more may benefit from this treatment. In a patient with subtotal liver involvement using local hyperthermia and chemotherapy with sequential use of FOLFOX, later FOLFIRI and later Capecitabine a nearly three-year survival could be achieved (Image 6).

In a patient with very advanced rectal cancer protruding out of the anus but no distant metastases using local hyperthermia and neoadjuvant FOLFOX first a very good partial remission could be achieved. Continuing local hyperthermia with neoadjuvant radiation plus Capecitabine finally a nearly complete remission was achieved. The patient could be operated in a way that normal bowel passage was achieved. Seven years later the patient is still free of disease (Image 7).

**Ovarian and cervical cancers:**

In ovarian and cervical cancer standard chemotherapy is Carboplatin and the neurotoxic drug Paclitaxel. Together with hyperthermia Carboplatin could be combined with the less toxic Cyclophosphamide which is a drug with enhancement of its activity under hyperthermic conditions (Image 8).

In a 28-year-old patient with very advanced inoperable ovarian cancer a complete remission could be achieved with whole body hyperthermia and Carboplatin in moderate doses (AUC 4-4,5) plus Cyclophosphamide resulting in survival until today, 9 years later (Image 9).

In patients with recurrent cervical cancer a combination of local hyperthermia and chemo-embolisation can be successful. By chemo-embolisation the perfusion of the tumor is reduced so that hyperthermia heats the tumor up more selected. In a patient with a very large cervical recurrence filling nearly the complete small pelvis, causing subtotal compression of the bladder requiring nephrostomas on both sides and heavy vaginal bleeding and pain as symptom a fast remission could be achieved with the patient free of symptoms. The nephrostomas could be exchanged to ureteral splints when the bladder got back its capacity (Image 10).

**Breast cancer:**

In breast cancer patients often are pretreated by neoadjuvant or adjuvant chemotherapy. Therefore, in patients with local recurrence or with metastases chemotherapy options are limited. Using a chemotherapy with moderate doses of Vinorelbine and Mitomycin a high rate of responses can be achieved. But whole-body hyperthermia also can be applied in the neoadjuvant situation (Image 11) but also in wide spread disease around the chest wall and around breast implants (Image 12).

In a small study we could show that between 70% and 80% of consecutive patients with breast cancer respond to a treatment program with whole body and local hyperthermia together with moderate doses of chemotherapy (image13).

Hyperthermia is a treatment which does not have dangerous side effects. Most patients tolerate it very well.

After local hyperthermia sometimes "hot spots" occur in fatty tissues. In whole body hyperthermia the risk of local superficial burns is about 4% (depending on the experience of the therapist).

**Discussion:**

Together with hyperthermia it is possible to use chemo-therapy in more moderate doses. This reduces toxicity and helps patients in particular in the palliative situation to preserve quality of life. It also allows to perform treatments more regular and over a longer period of time which possibly is very important to achieve longer survival times.

This report presents a number of patients with very advanced diseases difficult to treat. In all of these patients using standard treatment protocols similar responses would not have been expected.

International studies exist up to now for patients with cancer of the cervix uteri, for patients with sarcoma, for patients with recurrent breast cancer but also colorectal and ovarian cancer. However, the number of these studies is limited and often they are not performed in a randomized form.

Randomized studies on the other hand are difficult to perform nowadays as chemotherapy treatment guidelines change very fast, sometimes every year. So, performing a randomized study with hyperthermia using a certain chemotherapy protocol after 2 years would not be up-to-date anymore as other chemotherapies would be standard. Also

patients often don't accept to be randomized into the group without hyperthermia as they can see that nearly all studies about hyperthermia show improvement of response and survival time.

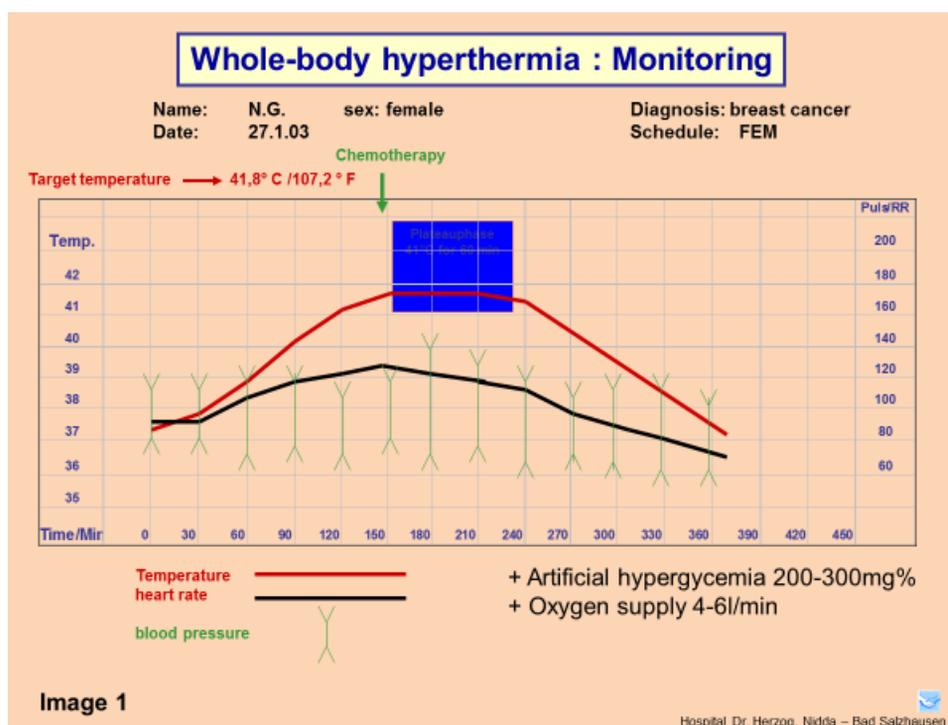
**Summary:**

Using hyperthermia, the efficacy of chemotherapy can be increased. This results in higher response rates. But it also enables to use more moderate chemotherapy doses resulting in less adverse effects and better quality of life. Hyperthermia together with chemotherapy is effective even in heavily pretreated patients.

Adverse effects are few, however, the rate of side effects depends on the experience of the treating physician.

Many studies about hyperthermia have been published in the last 30 years. But further studies are necessary to better evaluate the best timing of hyperthermia and the best chemotherapy protocols.

Hyperthermia is a relatively cheap treatment compared to the cost of modern oncological treatments. As it allows to use chemotherapies in more moderate doses and using cheap and well researched older chemotherapy drugs it is a treatment option to escape the spiral of increasing cost in oncology.



## Standard chemotherapy in ENT-cancers

- Cisplatin	20mg / m <sup>2</sup>		d1 – d5
- 5-FU	600mg / m <sup>2</sup>	cont. infus.	d1 – d5
- Mitomycin	10mg / m <sup>2</sup>		d1
- 5-FU	600mg / m <sup>2</sup>	cont. infus.	d1 – d5
		(repeat d29)	

### chemotherapy with hyperthermia

- Cisplatin	50mg / m <sup>2</sup>		d1 + d4
- 5-FU	1000mg / m <sup>2</sup>	chronomodulated over night	d1 – d4
		(repeat d29)	
- Mitomycin	8mg / m <sup>2</sup>		d1
- 5-FU	1000mg / m <sup>2</sup>	chronomodulated over night	d1 – d4
		(repeat d29)	

Image 2

Hospital Dr. Herzog / Bad Salzhausen

### Case report: local hyperthermia + Cisplatin/5FU in locally advanced Nasopharynx carcinom with metastases to the cervical lymph nodes

S.H., male, 59 years old

#### Pretreatments:

11/13 first diagnosis, inoperable tumor. Alternative therapies like Budwig Diet, Chinese tees.

#### Symptoms:

Headache, deafness right ear, epistaxis right side, pain behind the right eye

#### result:

subtotal remission, no pains any more. Persistent deafness right ear.



Image 3

Hospital Dr. Herzog, Nidda/Bad Salzhausen

**Whole-body- and local hyperthermia in NSCLC with solitary bone metastasis (adenocarcinoma, EGFR neg., ALK neg., PDL1 pos.) (Patient: SK, 58 years)**

**History:**

02/17 severe pain in the left shoulder, dry cough. Diagnosis of the disease

**Therapy:**

6 cycles Carboplatin/Gemcitabine in combination with whole-body-hyperthermia and local hyperthermia

**Result:**

PR, Strong shoulder without pain anymore, regrowth of bone, no cough anymore

**Continuation of treatment:**

Radiation in combination with local hyperthermia of the remaining lung tumour and the remaining shoulder metastasis

27.02.2017



19.07.2017



13.02.2017



19.07.2017

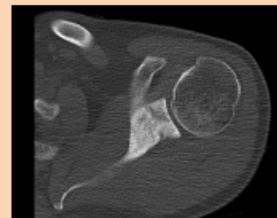


Image 4

Hospital Dr. Herzog, Nidda/Bad Salzhausen

**Standard chemotherapy in colorectal cancer**

- Oxaliplatin 85mg / m<sup>2</sup> or Irinotecan 180mg / m<sup>2</sup>
  - Calciumfolinat 200mg / m<sup>2</sup>
  - 5-FU bolus 400mg / m<sup>2</sup>
  - 5-FU over 46h 2400mg / m<sup>2</sup>
- (repeat d15)
- 
- Capecitabine 2500mg / m<sup>2</sup> / day
- (2 weeks on / 1 week off)

**chemotherapy with hyperthermia**

- Oxaliplatin 85mg / m<sup>2</sup> or Irinotecan 120mg / m<sup>2</sup>
  - Calciumfolinat 200mg total d1 + d2
  - 5-FU 1000mg / m<sup>2</sup> d1 + d2 chronomodulated over night
- (repeat d15)
- 
- Capecitabine 1800mg / m<sup>2</sup> / day
- (2 weeks on / 1 week off)

Hospital Dr. Herzog, Nidda-Bad Salzhausen

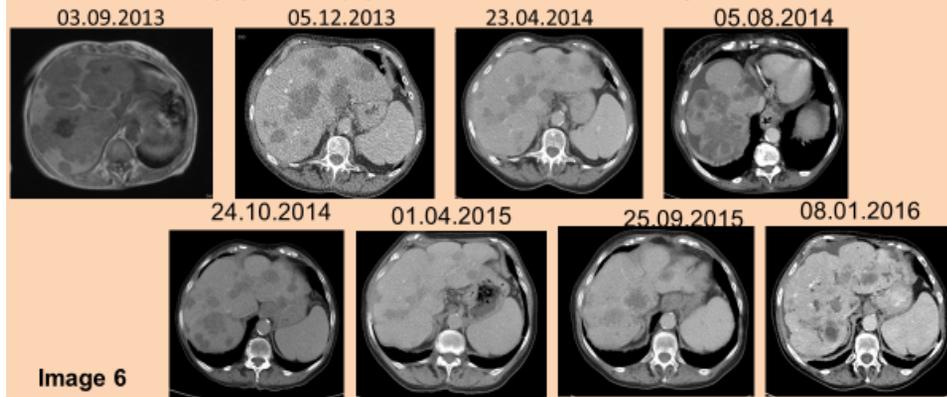
Image 5

**Local hyperthermia in metastatic rectal cancer** Patient: S. A.-A., 74 years old Hospital Dr. Herzog, Nidda/Bad Salzhausen

**diagnosis:** Rectal cancer with subtotal destruction of the liver by metastases  
**Symptoms:** weakness, abdominal pain, subtotal rectal obstruction, dislocated rectal stent, predicted survival weeks  
**Treatment:** local hyperthermia + Folfox, later Folfiri, later Xeloda, later rechallenge Folfox

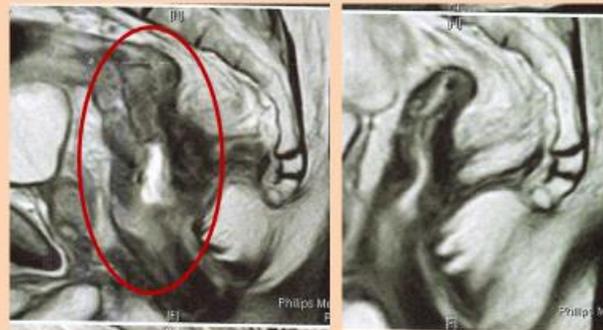
	09/2013	02/2014	01/2015	06/2015
Ca 19- 9	5124 U/ml	55.6 U/ml	20.7 U/ml	25.0 U/ml
CEA	3750 ng/ml	15.3 ng/ml	2.9 ng/ml	8.3 ng/ml

**Result:** very good PR. Normal bowel function again, no symptoms, Biopsy rectum: no cancer detectable any more



**Local hyperthermia in rectal cancer**

**patient:** G.C., 68 years  
**diagnosis:** rectal cancer  
**pretreatment:** 10/2003 first diagnosis, permanent colostoma suggested. Patient refused this treatment  
**symptoms:** 10/ 09 bowel obstruction, pain  
**therapy:** 10/09 colostoma, neoadjuvant Folfox + local hyperthermia  
**Results:** good PR, reduction of the pain



**Further treatments and outcome:**  
 07/10 neoadjuvant radiochemotherapy with Capezitabine + local hyperthermia  
 10/10 R0 resection, ypN1c (1/20)  
 01/11 reversal of colostoma  
 2017 No evidence of local recurrence or metastases



**Image 7**

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### Standard chemotherapy in ovarian cancer

- |                         |                        |    |
|-------------------------|------------------------|----|
| - Carboplatin           | AUC 5-6                | d1 |
| - Paclitaxel            | 175mg / m <sup>2</sup> | d1 |
| (repeat d22)            |                        |    |
| <hr/>                   |                        |    |
| - liposomal Doxorubicin | 50mg / m <sup>2</sup>  |    |
| (repeat d29)            |                        |    |

### chemotherapy with hyperthermia

- |                         |                        |  |
|-------------------------|------------------------|--|
| - Carboplatin           | AUC 4-5                |  |
| - Cyclophosphamid       | 600mg / m <sup>2</sup> |  |
| (repeat d29)            |                        |  |
| <hr/>                   |                        |  |
| - liposomal Doxorubicin | 20mg / m <sup>2</sup>  |  |
| (repeat every 2 weeks)  |                        |  |

Image 8

Hospital Dr. Herzog, Nidde-Bad Salzhausen



### Inoperable advanced ovarian cancer: Neoadjuvant chemotherapy in combination with whole-body-hyperthermia

Pat: S. E., 28 years old



after laparotomie 04/08



after 3 cycles of therapy 08/08

- history:** first diagnosis 3/08, at laparotomia inoperable situation, cystic tumour
- symptoms:** stomach, adynamia, pain and pressure in the abdomen
- therapy:** neoadjuvant whole body hyperthermia + Carboplatin/ Cyclophosphamid for 5 cycles (reduced dose because of hematotoxicity,) followed by radical ovar- and hysterectomy
- Result:** MRI: CR. At surgery 5 mm remaining tumour in the left ovar, adjuvant 2 more cycles
- 10/17:** **no evidence of disease**

Image 9

Hospital Dr. Herzog, Bad Salzhausen



**Local hyperthermia and regional chemoembolisation  
in locally recurrent cervical cancer** (Patient: RJ, age: 39 years)

**History:**

01/15 squamous cell cancer of the cervix uteri, pT1b, G3R0, radical hysterectomy  
03/17 local recurrence with subtotal involvement of the complete small pelvis, compression of the bladder, subileus. Placement of nephrostomas both sides because of hydronephrosis  
04/17 recurrent vaginal bleeding, transfusions required. Embolisation without success. Constant compressing vaginal tamponade necessary

**Symptoms:**

Recurrent bleeding, severe lower abdominal pain, subileus, compression of the urinary bladder. Nephrostomas both sides.

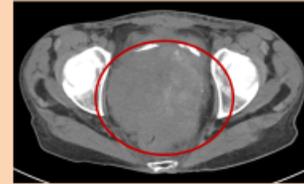
**Therapy 05/17:**

Local hyperthermia and regional chemoembolisation for 4 cycles (Mitomycin, Gemcitabine, Cisplatin)

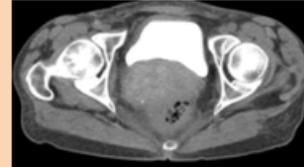
**Result:**

Reduction of tumour to 20%, no bleeding anymore, normal bowel movements, normal bladder filling again, change from nephrostomas to ureterstents (09/17)

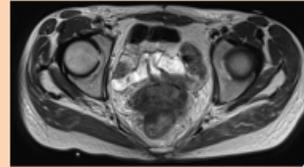
08.05.2017



01.06.2017



04.07.2017



**Image 10**

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**Neoadjuvant hyperthermia and chemotherapy in breast cancer**

Patient: L.B. 51 years

01.04.2016

**Previous treatments:**

07/14 First diagnosis of breast cancer HER-2 pos., alternative treatments and local hyperthermia without chemotherapy. Progression.  
04/16 breast tumor of 12 cm and axillary lymphadenopathy (cT3cN1). Mastectomy suggested.

**Symptoms:**

Painful swelling of the right breast, pain in the axilla.

**Therapie:**

Neoadjuvant chemotherapy with 4 cycles Vinorelbine and Mitomycin in combination with local and whole body hyperthermia, only first cycle with Herceptin. Very good PR.

**Further treatments:**

Breast saving surgery ypT1a ypN1a (3/3) G3. Maintenance treatment with Herceptin planned.



20.06.2016



**Image 11**

Hospital Dr. Herzog, Nidda/Bad Salzhausen

**Bilateral breast cancer with chest wall involvement, lymphatic, pleural and hepatic metastases**  
 Hospital Dr. Herzog, Nidda/Bad Salzhausen

patient:  
G.P., 45 years old

**History:**  
12/15 lump left breast, alternative treatment with black salve and vegan diet, progression with ulceration

**Situation:**  
11/16 large tumor masses, pain, shortness of breath. Lymphedema left arm

**therapy:**  
Whole body and local hyperthermia with Vinorelbine/Mitomycin, complementary treatments.

**result:**  
Very good partial remission already after 2 cycles. Ulcerations healed, lymphedema improved.

**Image 12**

