

Hyperthermia in Cancer Treatment: Scientific Evidence in Clinical Experience

Alexander Herzog¹

(1) Chief Physician of Fachklinik Dr. Herzog, Germany

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Hyperthermia as anticancer treatment has been researched in the last decades and many mechanisms of action could be clarified. Investigations at the cellular level but also in animal experiments could show beneficial activity of the hyperthermia against cancer disease. Also in studies in human beings it could be shown that the activity of standard cancer treatments like radiation or chemotherapy could be enhanced by simultaneous hyperthermia.

So in Germany the private health insurances cover the cost of hyperthermia in conjunction with chemotherapy and radiation. However, in many countries hyperthermia is not used or not covered by the insurances claiming missing evidence for benefit.

Hyperthermia on its way to evidenced based medicine

In the medical scientific literature there are many studies about hyperthermia fulfilling the criteria of a critical assessment of validity and utility. However, the level of evidence is not the same for all tumor types. As for each type of tumor separately the proof of benefit of hyperthermia has to be shown the actual level of evidence depends on the studies performed up to now on specific cancer types. There also are differences using different devices or technologies of hyperthermia.

Hyperthermia and radiation in cancer of the cervix uteri

The combination of hyperthermia and radiation in cervical cancer belongs to the hyperthermia treatments mostly researched in randomized studies. In different studies it has been shown that performing hyperthermia in addition to radiation in advanced cervical cancer the rate of complete remissions could be increased from 57 % to 87% and the 3- years survival could be increased from 37 % to 51 % (Van de Zee et al, Lancet 2000). So in Holland this treatment combination is used as standard treatment for advanced cancer of the cervix. There is a picture what shows a patient with an advanced cancer of the cervix before and after combined local hyperthermia and radiation.

Hyperthermia in breast cancer

Also in a treatment of locally recurrent breast cancer there are studies showing benefit of local hyperthermia in combination with a second-line radiation. In a Meta-analysis of 5 studies using different techniques of hyperthermia it could be shown that the local tumor control could be improved by 35 % (Vernon et al, Int J. Radiat. 1996). Phase II studies showed a complete remission in up to 50 % of the cases (Bicher et al, Int. J. Radiat. Oncol. 1986). As in the situation of recurrent breast cancer the disease frequently is already systemic also whole body hyperthermia in combination with chemotherapy could be considered.

In an own small study in patients with metastatic breast cancer we achieved in 75 % of the cases a partial remission after whole body hyperthermia and chemotherapy (Herzog, Komplement, 2002).

Hyperthermia in ovarian cancer

Ovarian cancer is a tumor of the abdominal cavity. So local hyperthermia in these cases doesn't reach all abdominal tumors. More aggressive local approaches to treat the abdominal cavity with hyperthermia is the HIPEC treatment (hyperthermic intra- peritoneal chemotherapy).

In a study combining whole body hyperthermia with chemotherapy in the Dolphin Study from Munich successful results could be shown with a remission in 50 % and stable disease in 42% of the patients (Strobel et al, Dolphin Studie, ASCO 2002).

There is a picture what shows an impressive case of an inoperable patient who we treated with whole body hyperthermia and chemotherapy (Carboplatin/Cyclophospharnid). The tumor masses

could be reduced down to a 5 mm remaining tumor in the left ovary which completely could be removed in a second look surgery. 5 years later the patient still is free of disease.

Hyperthermia in ENT-tumors

ENT-tumors frequently grow locally. They can be reached well using local hyperthermia. There are randomized studies showing an improved activity of a combination treatment of hyperthermia and radiation compared to radiation alone. Interestingly this mainly is valid for advanced stages. But also a combination of local hyperthermia and chemotherapy can be efficient in ENT-tumors. There is a picture what shows a patient who after several recurrences and pretreatments like radiochemotherapy and several surgeries a treatment combination of chemotherapy and local hyperthermia could achieve a complete remission lasting for 4 years. Also another patient with cervical lymph node metastases of a squamous cell cancer of the tonsil a combination of chemotherapy and local hyperthermia could achieve a lasting complete remission. This patient had refused radiation as she didn't want to go through radiation- induced side effects.

Hyperthermia in rectal cancer

There is one randomized study showing improved remission rates from 49 to 66% and prolonged time to recurrence from 20 to 28 months when a neoadjuvant radio-chemotherapy was combined with local hyperthermia (Rau et al, Schweiz. Rupdsch. Med. Prax. 2001). An own case report shows a patient who had suffered from a slowly growing rectal cancer for more than 7 years finally with penetration through the anus. After neoadjuvant radio-chemotherapy and local hyperthermia the tumor masses could be reduced that much that surgery could be performed finally maintaining a normal stool passage.

Hyperthermia in brain tumors

About the treatment of brain tumors with hyperthermia up to now there are no randomized studies available. But there are published case reports showing that also in these conditions a successful treatment is possible. In one of our cases, a patient with an advanced Oligodendroglioma grade II which had been progredient after several pre-treatments in an experimental approach combining regional chemoperfusion of the tumor (Prof Vogl, University hospital of Frankfurt) and local hyperthermia a surprising good response and disappearance of the symptoms could be achieved.

Evidence of hyperthermia

Considering the number and the quality of the published studies the level of evidence of hyperthermia treatment can be established (Image 8). Following the evidence criteria there is evidence level A for diseases like advanced cancer of the cervix uteri, recurrent breast cancer, esophagus cancer and ENT-tumors. According to the criteria of evidence there is a grade of recommendation A for the use of hyperthermia. For local recurrent rectal cancer, malignant melanoma and sarcomas there is at least one randomized controlled study. So also here the grad of evidence A may be assumed. In other tumors up to now there is no higher level of evidence but there is grade of recommendation B or C for the treatment with hyperthermia.

Conclusion

As conclusion can be stated, that the criteria of evidence based medicine for hyperthermia for several types of disease are fulfilled with high grade of recommendation as there are many randomized and not randomized studies. In other oncological diseases there are well documented positive case reports and experiences. In these diseases further research is necessary.