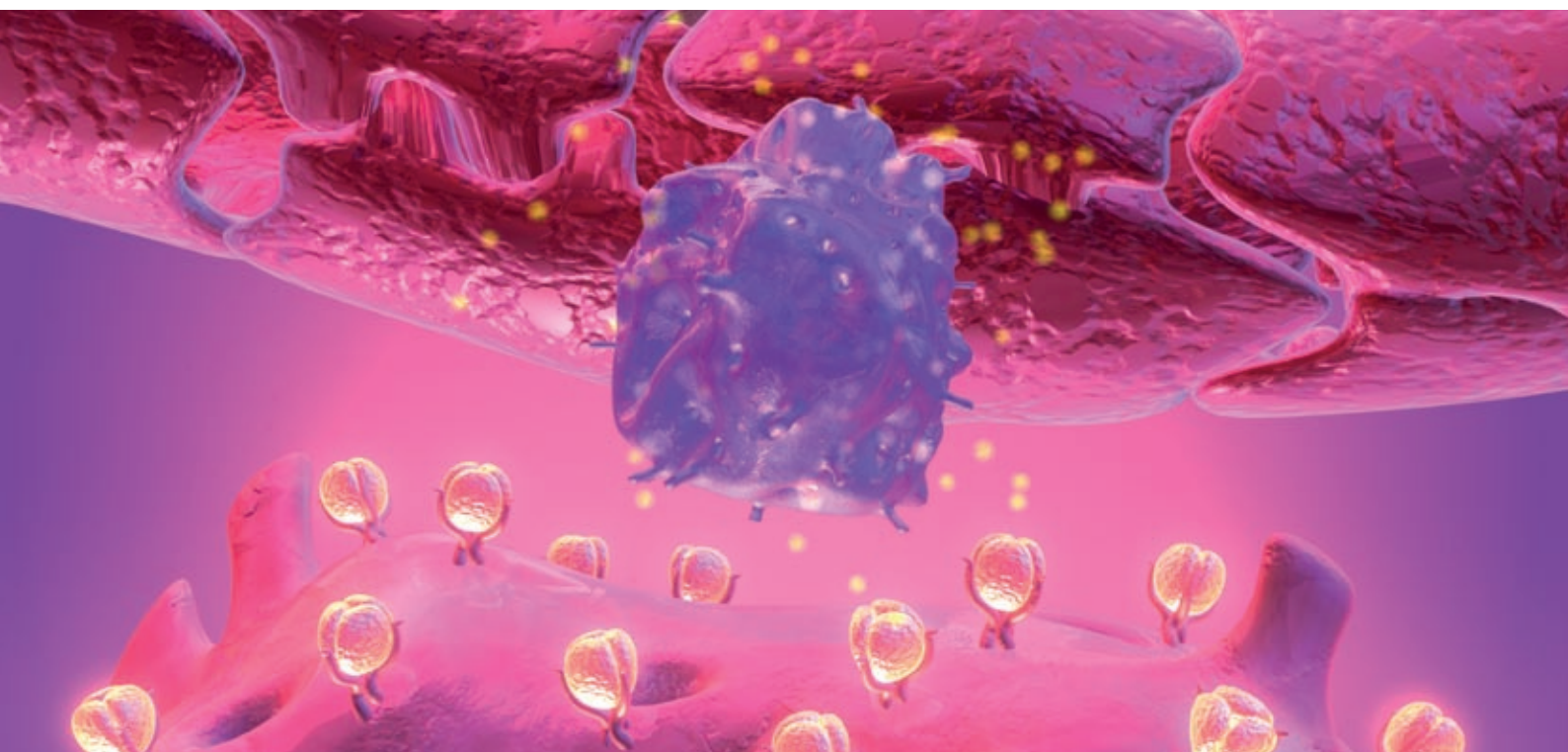




Hyperthermia as the Fourth Column in Oncology

Scientific principles of heat therapy



Hyperthermia as the Fourth Column in Oncology

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Therapeutic gains from hyperthermia

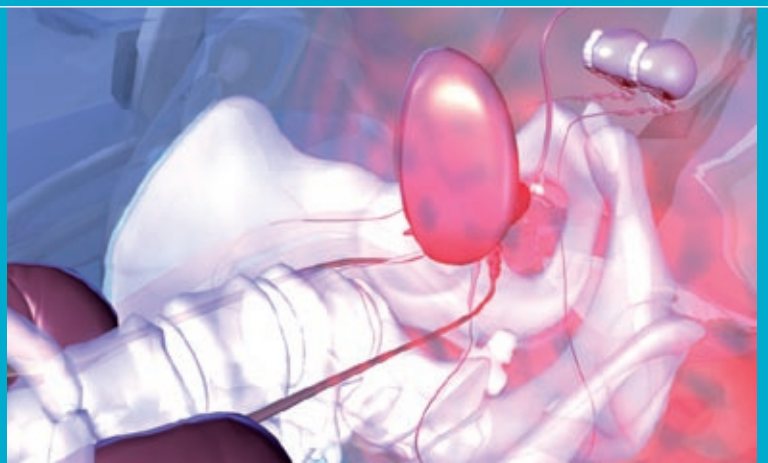
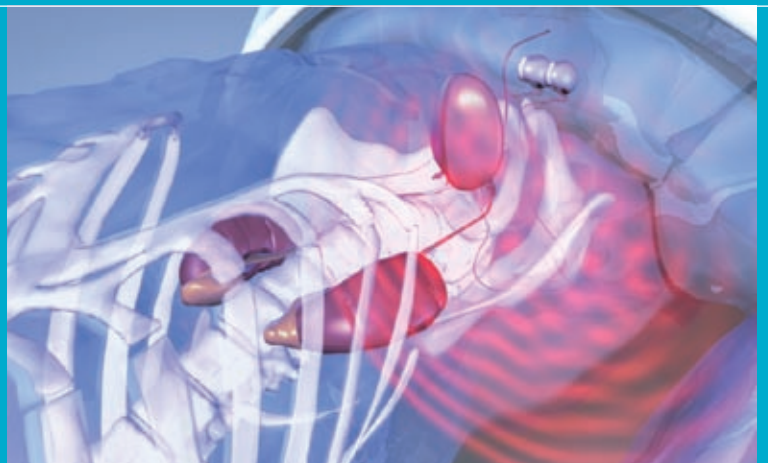
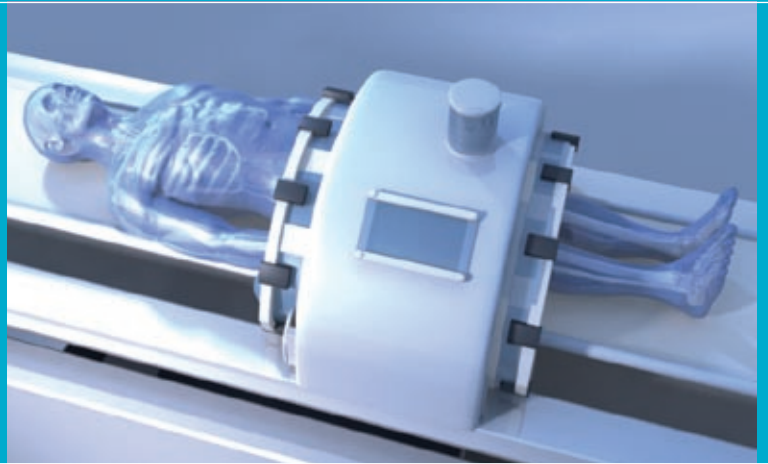
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The Heat is on



Hyperthermia as the Fourth Column in Oncology

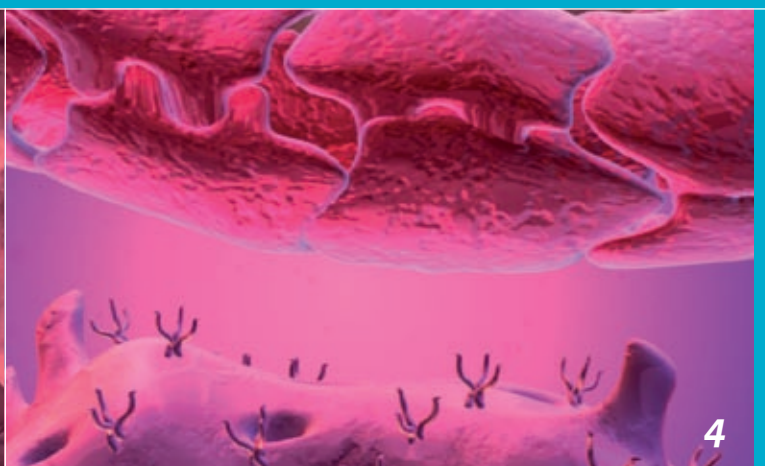
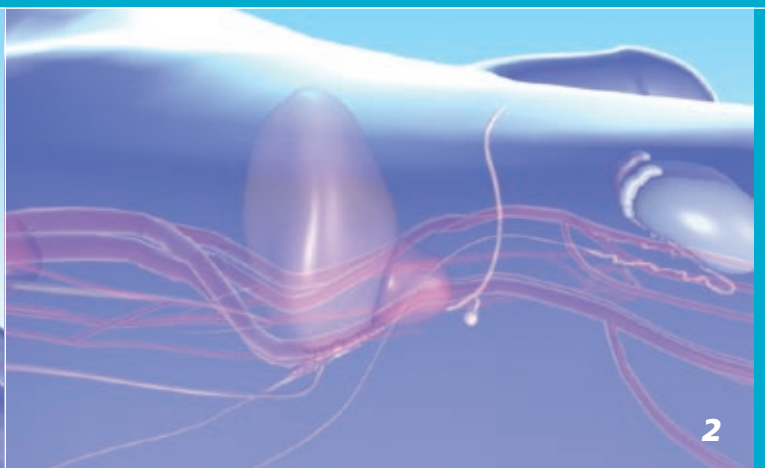
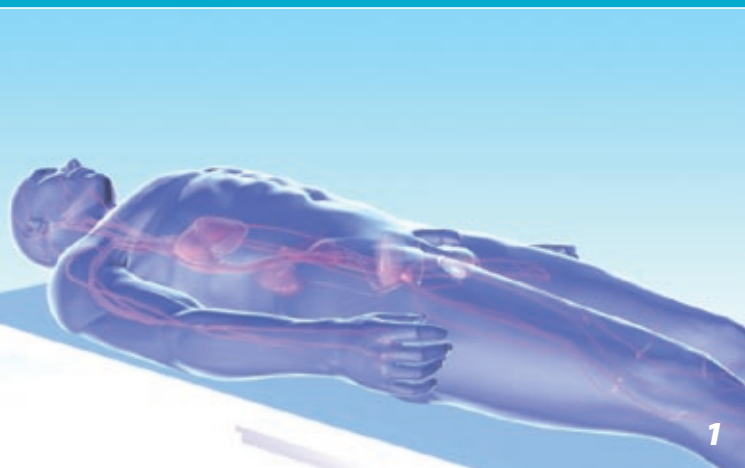
> Scientific principles of heat therapy

“The Heat is on in Oncology” – research and the clinical application of heat therapy is currently being dynamically promoted under this slogan. While just a few years ago hyperthermia was considered a dubious therapeutic approach with an unproven effect, today numerous renowned university hospitals are using this technically sophisticated procedure for fighting cancer. It is a procedure that – and this is important to note – used in combination with standard cancer therapies only, can extend more lives than many of the medications developed over the last few years.

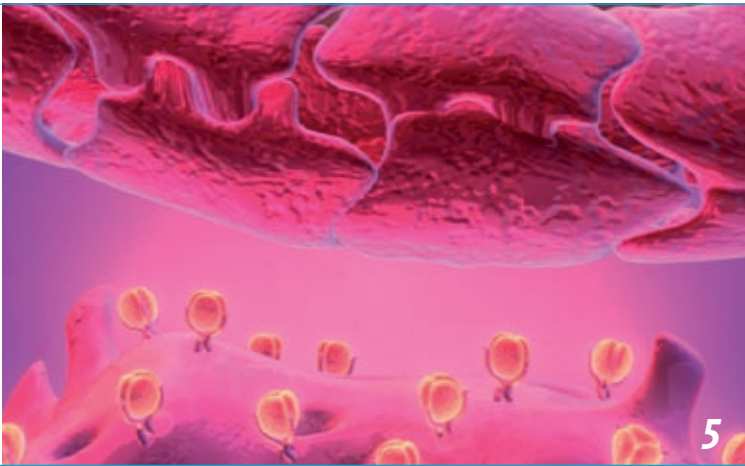
Radio frequency-induced hyperthermia can significantly increase the survival rate of cancer patients. In Phase III studies, where hyperthermia was combined with radiation therapy and/or chemotherapy, hyperthermia improved the two-year local tumor control results for high-risk sarcoma from 12% to 37% and for melanoma from 28% to 46%;

increased complete remission for breast cancer recurrence from 38% to 60%; an increase in two-year survival rate for glioblastoma from 15% to 31%; and an increase in complete remission of advanced cervical carcinoma from 57% to 83%, compared with radiation therapy or chemotherapy alone.

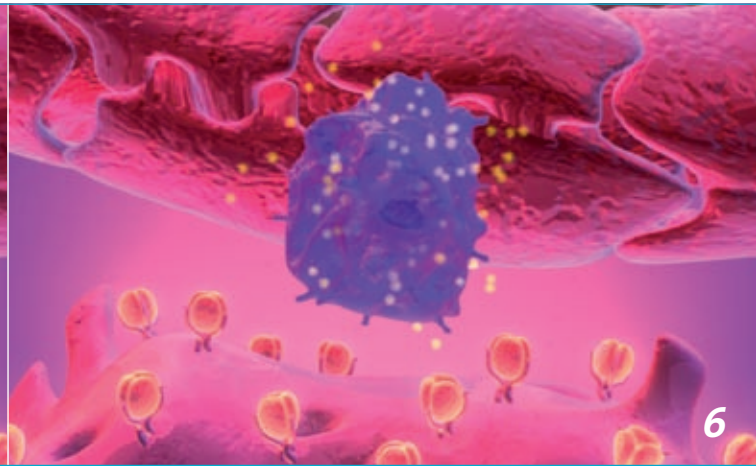
The Heat is on



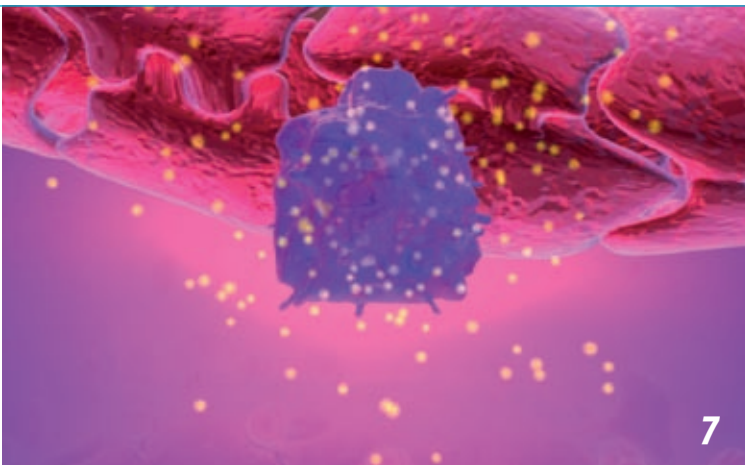
The Heat is on



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6



7

The actual heating, hyperthermia, is generated by transmitting the radio waves into the tissue. After a short while, thermal shock proteins emerge on the tumor cell surface. As a consequence, immune system cells are activated and can efficiently destroy the tumor cells that carry such thermal shock molecules.

The fight against cancer

Enhancing standard therapies

Weaknesses in malignant tumors

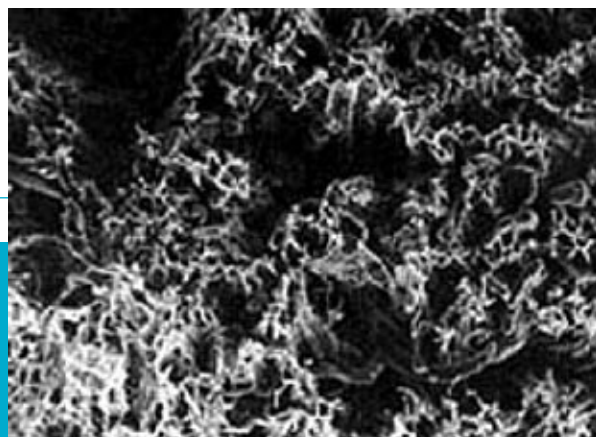
> Chaotic blood vessels, hypoxic cells

Malignant tumors result from the growth of mutated cells, which require more energy to survive than normal cells. The existing blood vessels that provide nourishment and oxygen for the cells provide insufficient energy for the uncontrolled multiplication of these cells. For this reason, malignant tumors stimulate the growth of additional blood vessels. However, these new blood vessels exhibit chaotic structures, when compared to blood vessels in normal tissue. They are of an unusual size and have kinks and dead ends. Often, large areas of tumors are hypoxic because of the irregular structure of these blood vessels. And because hypoxic cells cannot sufficiently eliminate contaminants via the blood, they exhibit a lower pH value.

Additionally, significant changes in perfusion can often be observed with these tumors because the unstable blood vessels periodically collapse and deprive the cells of oxygen. It is extremely difficult to kill oxygen-deficient cells with ionizing radiation (which forms oxygen radicals that attack DNA) or chemotherapy (which requires blood flow to transport the cytostatic agents). Because hypoxic cells tend to metastasize, their destruction is a high priority in cancer treatment.



Mutated blood vessels from cancerous tissue



Normal blood vessels in healthy tissue

How hyperthermia helps

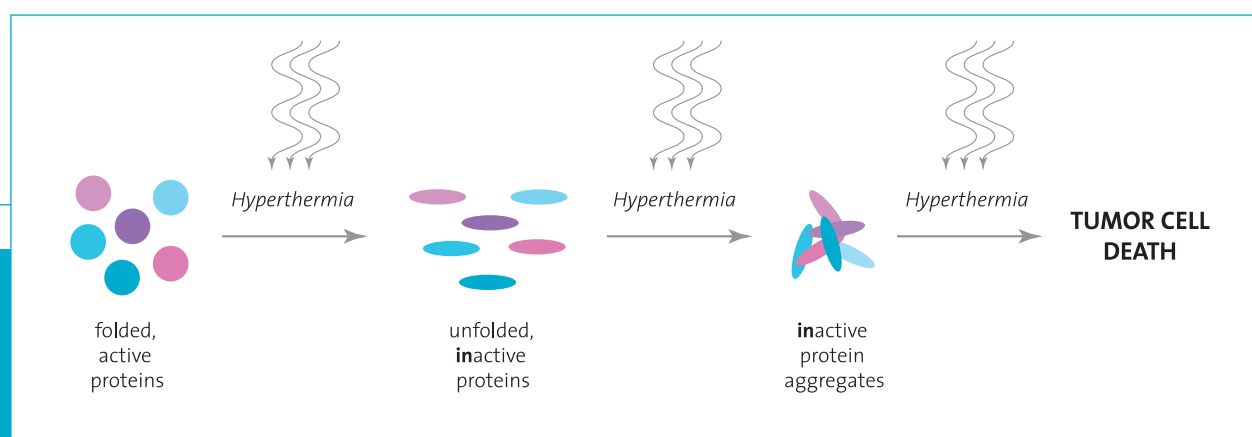
The effect of hyperthermia at the biochemical level

> Attack on overacidified cells

Hyperthermia destroys cancer cells by raising the temperature in the cell to between 41.5°C and 43°C. It takes advantage of the weaknesses in malignant tumors described above. Since the body reduces temperature through perfusion, tumors with low or irregular perfusion remain at a higher temperature level during hyperthermia, while the surrounding normal tissue, with regular perfusion, remains at a lower temperature.

This is the result of their inability to eliminate anaerobic metabolites. Hyperthermia attacks the overacidified cells, breaches the stability of the cellular proteins, leads to their aggregation, finally resulting in cell death.

Science attributes the death of cancer cells at hyperthermic temperature to damage of the plasma membrane, the cell skeleton, and the cell nucleus. Cancer cells are particularly susceptible to hyperthermia treatment due to their high acidity.



Biochemical mode of action of hyperthermia

The perfect partnership

Hyperthermia and radiation therapy

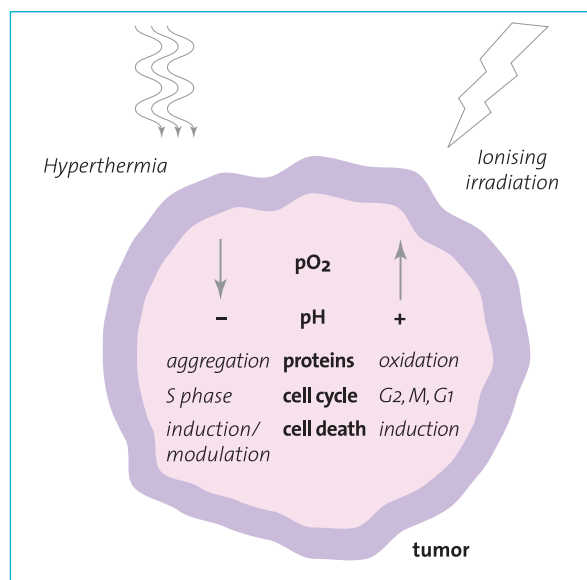
Why hyperthermia increases the efficacy of radiation therapy by up to a factor of five

> Improved perfusion and oxygen supply

Hyperthermia and radiation therapy complement one another. The thermal stimulus associated with hyperthermia treatment causes improved blood circulation and therefore improved oxygen supply to the tumor. This is important for increasing the efficacy of radiation therapy. Ionizing radiation destroys cancerous tissue primarily through the generation of oxygen radicals that attack the DNA of the cancer cells. Tumor cells containing insufficient oxygen are three times more resistant to ionizing radiation than normal cells. Thus, there is a direct relationship between hypoxia in human tumors and radiation therapy failure. Conversely, the higher the oxygen content in the cancerous tissue, the more effective the radiation therapy.

In addition to the creation of oxygen radicals that attack cancer cell DNA, hyperthermia also causes the accumulation of proteins in the cell nucleus. This prevents the self-repair of cancer cell DNA that is damaged by the ionizing radiation. In addition, ionizing radiation and damage cells during different phases of the cell cycle. Tumor cells are resistant to ionizing radiation during the synthesis phase, but they are susceptible to the destructive effects of hyperthermia during this phase. Poorly perfused tumor tissue that is resistant to ionizing radiation is susceptible to hyperthermia.

In contrast, tumor tissue with good blood circulation does not react to the heat, but is susceptible to ionizing radiation. This complementary interaction is a compelling reason for combining hyperthermia and radiation therapy (thermoradiotherapy). *In-vivo* studies have shown that the use of hyperthermia can increase the effects of radiation therapy by a factor of between 1.2 and 5. This means that hyperthermia is one of the most effective potentiators of radiation therapy.



Synergistic mode of action of radiotherapy and hyperthermia

The perfect partnership

Hyperthermia and chemotherapy

Why hyperthermia significantly increases the efficacy of cytostatica

> Activating chemical reactions

Hyperthermia can also significantly increase the effectiveness of chemotherapy. As with radiation therapy, the primary reason is increased perfusion in the tumor tissue. The improved blood flow simplifies the uptake of cytostatica through the cell membranes. In addition, the increased temperature functions as an activator for the drug therapy because the chemical reactions are accelerated by the heat.

When treating large tumors in particular, hyperthermia represents an ideal supplement to chemotherapy. Often, the center and other regions of cancer foci of large tumors have poor blood circulation, retarding cell growth. As a result, they are not reached by cytostatica that primarily attack quickly dividing cells. Hyperthermia significantly increases the perfusion of the tumor cells and therefore the uptake of the drug.

Numerous publications have described the interactions between hyperthermia and various cytostatica, such as doxorubicin, mitomycin C, mitoxantrone, bleomycin, cisplatin, nitric acid, uric acid, and cyclophosphamide. Heat therapy has been shown to make resistant tumors responsive to cytostatica.

Hyperthermia has been used with liposomes to target release of the cytostatica directly in the tumor. The cytostatica are into the liposomes, tiny spheres of fat. Using an intravenous drip, these liposomes are injected into the patient's blood. When they reach a part of the body that has been warmed to 42°C the liposomes melt, releasing their contents. This enables large quantities of chemotherapy drugs to be delivered directly to the tumor, significantly reducing side effects.

Promising research results

New perspectives

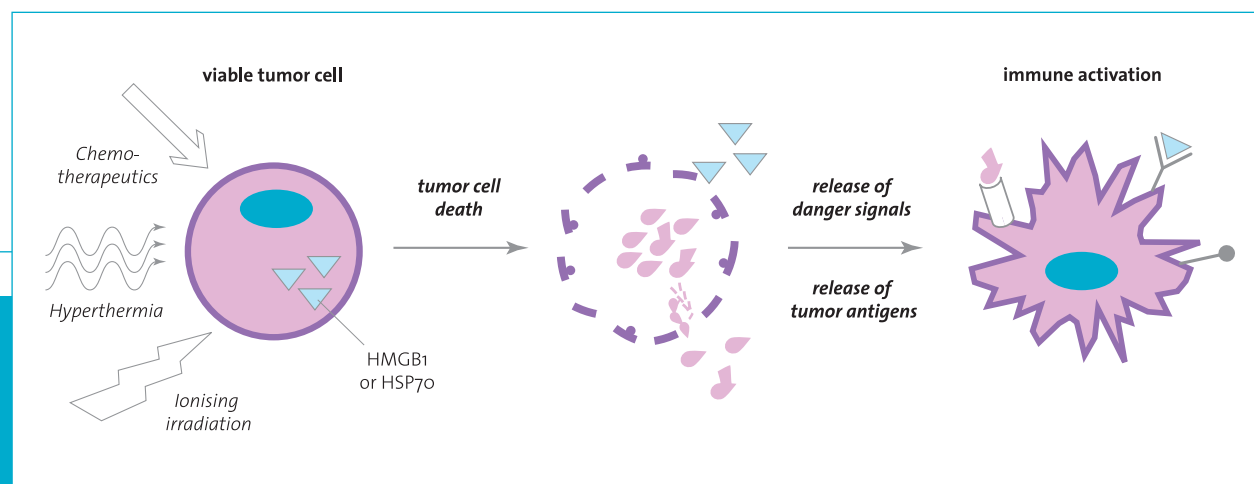
Hyperthermia and biological therapies

> Heat shock proteins and angiogenesis inhibitors

In **gene therapy**, hyperthermia appears to be an activator for new forms of biological therapy because gene production occurs a thousand times faster due to the heat (heat-moderated gene therapy).

For **immunotherapy** and the development of anti-tumor vaccines, hyperthermia plays a critical role. Heat puts cancer cells under stress. This results in the formation of heat shock proteins (e.g., HSP70) and cellular danger signals that in turn activate the immune system. This knowledge is the basis for the many research projects focused on how to develop immunotherapies using these heat shock proteins, and how to combine various vaccination methods with hyperthermia.

With respect to **antiangiogenesis**, research results indicate that hyperthermia contributes here as well because it blocks the formation of new blood vessels. As a result, it is suitable as an accompanying therapy to angiogenesis inhibitor drug therapy for surviving tumor cells in low perfusion regions.



Immune activation induced by hyperthermia

Improved patient well-being

Why hyperthermia simplifies surgery

> Dramatic shrinkage of tumors

Because it kills many cells, hyperthermia treatment often dramatically shrinks tumors, making surgical removal of the tumor easier or, in some cases, possible. Hyperthermia offers enormous pre-surgical therapeutic value, especially when resection of the tumor would be dangerous or impossible due

to its proximity to sensitive structures. Additional advantages of hyperthermia include fewer disfiguring surgeries in visible areas of the body; e.g., tumors in the head and neck area, if tumors are shrunk prior to surgery.

Hyperthermia and quality of life

> Fewer side effects, less pain

Many studies show that the quality of life of cancer patients is substantially improved when radiation or chemotherapy is combined with hyperthermia treatment. The combined treatment results in a significant, long-lasting reduction in side effects.

Hyperthermia stimulates the immune system and helps the body recover from the toxic side effects of standard therapies. And even in palliative cases, patients benefit from hyperthermia, as it alleviates bleeding, pain, and infection.

Clinical studies

Results of major studies

> Significant tumor reduction and extension of life

Over the last 15 years, 34 clinical studies (17 phase I or II, 17 phase III) have been published regarding the effects of hyperthermia combined with radiation therapy and/or chemotherapy. The following studies are the most important studies from leading European and North American research centers.

Superficial tumors

In 1996, *Cancer*, the international journal of the American Cancer Society, reported a clinical study of 23 patients with head and neck tumors, breast carcinomas, and malignant melanomas, which was conducted by Mayer and Hallinan at Johns Hopkins Hospital (USA). The results showed complete remission in 89% of patients and demonstrated that 74% of patients were free of local recurrence after two years. All patients were treated with hyperthermia and brachytherapy. The authors concluded that “outpatient treatment of human neoplasia with interstitial thermoradiotherapy can be performed practically, and is safe and effective” (refer to 77/11, pp. 2363–2370).

In 2005, a randomized Phase III study on hyperthermia and radiation therapy for the treatment of superficial tumors, which was conducted by Ellen Jones et al., was published in the *Journal of Clinical Oncology* (vol.23, no.13, pp.3079-3085). The majority of the 109 patients in the study had a breast wall recurrence. The other patients were suffering from head and neck tumors or melanomas. In patients who received hyperthermia combined with radiation, complete remission was observed in 66% of cases, compared to 42% of patients who received radiation alone. The effect was even greater among patients who had previously undergone radiation. In this case, 68% of those who received hyperthermia and radiation experienced complete remission, compared to 24% who received radiation alone.

Head and Neck tumors

In 1993, the *International Journal of Radiation Oncology, Biology, Physics* reported on the results of a Phase III study by Valdagni and Amichelli at Ospedale S. Chiara in Trento, Italy, conducted on 41 patients with inoperable stage IV head and neck tumors. The results of the study showed that the combined treatment with hyperthermia and radiation therapy increased complete remission from 41% to 83%, local recurrence-free survival from 24% to 68%, and the 5 year survival rate from 0% to 53%, compared with radiation therapy alone (refer to vol.28, pp.163-169).

Malignant melanoma

In 1996, the results of a multi-centric Phase III study with recurrent or metastasizing malignant melanoma (performed by Overgaard, Aarhus, Denmark, et. al.) was published in the *International Journal of Hyperthermia*. The study showed that hyperthermia combined with radiation therapy increased the complete remission rate from 35% to 62% and recurrence-free survival after 5 years from 28% to 46% compared to radiation therapy alone (refer to vol.12, no.1, pp.3 – 20).

Clinical studies

An internationally proven therapeutic approach

Breast carcinoma

The results of a multi-centric clinical Phase III study that included 306 patients with superficial localized breast carcinoma were published in 1996 by Vernon, Hand, Field, et.al (London, Great Britain) in the *International Journal of Radiation Oncology, Biology, Physics*. The results showed that the rate of complete remission increased from 41% to 59%, and the recurrence-free survival rate from 30% to 50%, when comparing the combined hyperthermia and radiation therapy treatment with radiation therapy alone (refer to vol. 35, no., 4, pp.731-744).

Glioblastoma

The results of a clinical Phase III study (performed by Sneed, Stauffer, McDermott, et. al. at the University of California, San Francisco, USA) on 112 patients with glioblastoma multiforme was published in 1998 in the *International Journal of Radiation Oncology, Biology, Physics*. The study showed a doubling of the 2-year survival rate when combining hyperthermia and brachytherapy compared with brachytherapy alone (refer to vol. 40, no. 2, pp. 287 – 295).

Soft-tissue sarcoma

Promising results of a randomised Phase III multicentre study dealing with high-risk soft-tissue sarcoma (Management: Rolf Issels, University Hospital Großhadern, for the „European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)“ and for the „European Society for Hyperthermic Oncology (ESHO“) and including 341 patients were already presented at the ASCO meeting 2007. The patients were treated before and after surgery with chemotherapy alone or with addition of regional hyperthermia, both followed by radiotherapy. The results were published online in *Lancet Oncology* in April 2010. The results are clear and significant: The overall response after induction therapy was more than twice as high in the combined

treatment group (plus hyperthermia) compared with the only chemotherapy treated group (28,8% versus 12,7%). The median duration of disease-free survival was prolonged for 14 months in the hyperthermia treated group compared to the control group (32 versus 18 month). Patients with signs of early disease progression and who received a consequent neo-adjuvant combination therapy with hyperthermia showed significant advantages in overall survival.

Tumors in the pelvis

A clinical Phase III study by van der Zee, Gonzalez Gonzalez, van Rhooon, et. al. (Rotterdam and Amsterdam, The Netherlands) on 358 patients with local, advanced tumors in the pelvis was published in *The Lancet* in 2000. The study showed that the combination of hyperthermia and radiation therapy increased the rate of complete remission for bladder carcinoma from 51% to 73%, and for advanced cervical carcinoma from 57% to 83%. The three-year survival rate in the hyperthermia and radiation therapy study group was 51%, compared to 27% for the group with radiation therapy alone (refer to vol.355, pp.1119–1125).

Cervical carcinoma

Martine Franckena from the Erasmus Medical Center at the University of Rotterdam published a study, which appeared in *Int J Radiat Oncol Biol Phys*. 2008 Mar 15;(4), in which patients with cervical carcinoma who were treated with or without hyperthermia were observed over a period of twelve years. The study showed that only 20% of those who had received radiation therapy alone survived; however, 37% of the women who received hyperthermia combined with radiation therapy were still alive. This highly significant result showed for the first time that the advantage of hyperthermia was not limited to a short period of time, but rather had long-term effectiveness.

Added benefits

One step further

Therapeutic gains from hyperthermia

In summary, clinical studies and experience have shown the following therapeutic gains from hyperthermia:

- Improvement in survival rates
- Improvement in local tumor control and the duration of local tumor control
- Increased remission rates
- Reduced morbidity
- Direct destruction of the tumor cells
- Improved palliation and durability of palliation
- Improved quality of life
- Increased effectiveness of other forms of treatment, without increased toxicity
- Improvement in tumor oxygenation, which increases the effectiveness of radiation therapy
- Destruction of both heat sensitive and radiation-resistant cells
- Improvement in the response rate to cytostatica
- Specific activation of the immune system
- Expansion of the treatable range of tumors in terms of size and status
- Increased uptake of cytostatica in cells
- Synergistic interaction with cytostatica
- Destruction of chemotherapy-resistant cells
- Activation of gene therapies
- Reduction in tumor size to enable resection and/or make resection safer
- Reduced disfiguration due to surgical tumor resection
- Improvement in functional results after surgery
- Increased effectiveness in patients who have received previous radiation therapy
- Improved results when combined with radiation therapy and chemotherapy (thermoradiochemotherapy)

Hyperthermia worldwide

Hyperthermia sponsors and centers

From research to clinical application

The National Cancer Institute (USA) has recognized hyperthermia as a treatment method for cancer, and is promoting research, development, and further advancement with tens of millions of dollars.

European institutions were just as generous. Deutsche Krebshilfe (German Cancer Aid) made it a top priority to declare hyperthermia to be a new, effective treatment against cancer, and the Deutsche Forschungsgemeinschaft (German Research Foundation) is one of its most important promoters.

Dutch health insurers financed a definitive study on the treatment of pelvic tumors with hyperthermia. The European Organization for Research and Treatment of Cancer (EORTC) ensures the quality of hyperthermia research in Europe and sponsors hyperthermia studies.

Many of the devices and equipment used worldwide for hyperthermia research and therapy were developed and manufactured by BSD Medical Corporation.

Additional information regarding hyperthermia, its indications, and certified centers where it is used, is available on our website:

www.sennewald.de



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