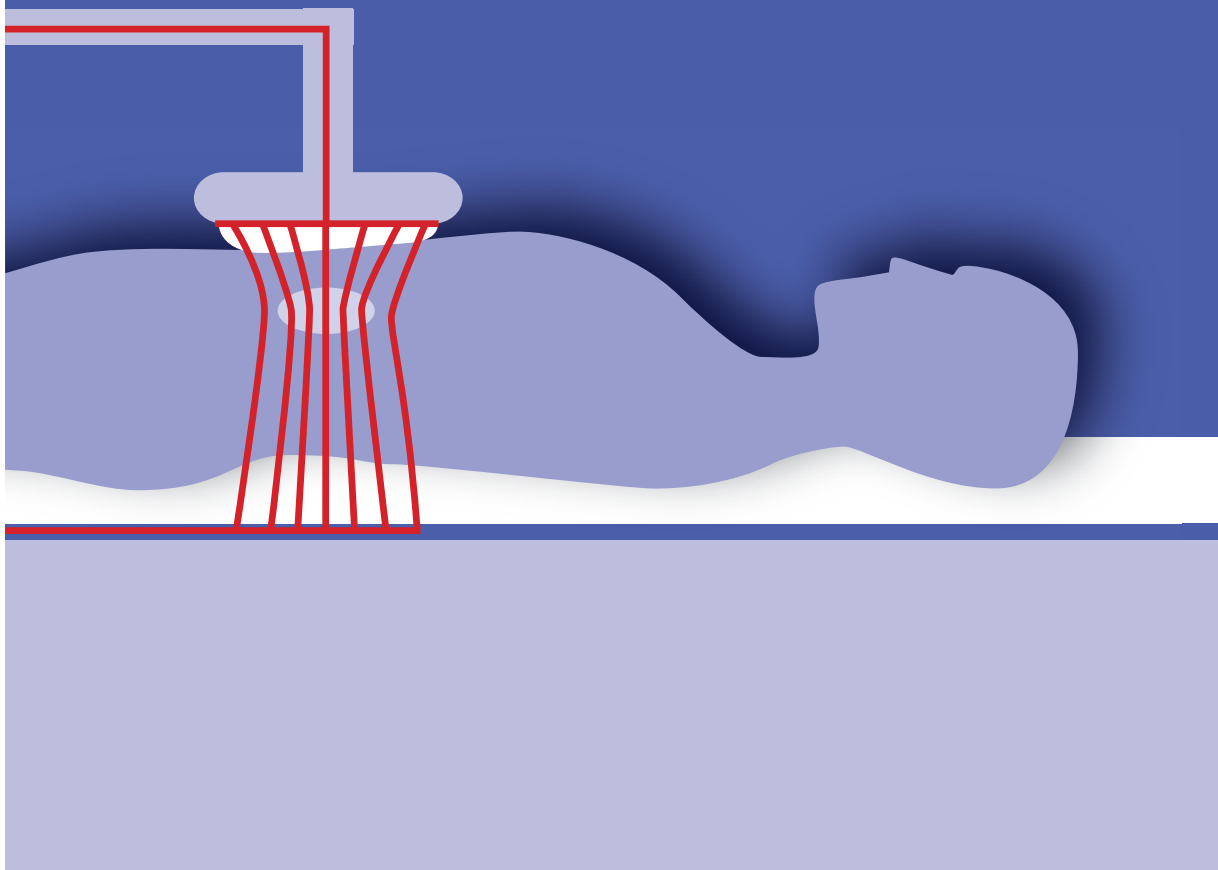


Oncothermia

Complementary medical therapy
in the fight against cancer



Oncotherm – About us

Oncotherm develops, manufactures and markets cancer treatment systems that apply a non-toxic therapy method and promote the body's natural regulatory processes. Their purpose is to heal cancer, to increase cancer patients' life expectancies and to improve patients' quality of life.

Oncotherm was founded in 1988 by Prof. Dr. András Szász, as a spin-off entrepreneurship based on research conducted at Eötvös Science University, located in Budapest. The electro-hyperthermia method was a completely new development in cancer treatment. Since its initial development, the medical and technical aspects of the method have been steadily improved, in accordance with the latest medical, scientific and technological findings. In the process, the method, now generally referred to as "Oncothermia", has become one of the leading Hyperthermia-based therapies in Europe. At present, more than 100,000 Oncothermia treatments are provided worldwide every year, to patients with many different types of tumor disorders.



Dr. Olivér Szász, managing director of the Oncotherm Group, and Prof. Dr. András Szász, founder and scientific consultant

The Oncotherm group has two locations, one in Hungary and the other in Germany, with both offices working closely together to promote the quality of their products and the further development of Oncothermia therapy. The German branch in Troisdorf mainly handles marketing and sales. Our young and dynamic team in Germany serves our customers, presents and represents our company at trade fairs and exhibitions, and organizes the yearly Hyperthermia Symposium that is held in Cologne for Oncothermia users and potential users. The team includes a service technician who remains available to our customers for assistance on technical questions. At our Budapest location, a team of highly qualified engineers and scientists focuses on technological and production-related aspects of the company's operations.

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R&D at Oncotherm

In Budapest, the Oncotherm founder and scientific consultant, Prof. Dr. Szász, heads a team of highly qualified scientists and engineers that conducts research and development in cooperation with university hospitals, large private clinics and postgraduate students.

Along with development of new product concepts and prototypes, scientific in-vitro and in-vivo studies are essential to the further development of Oncothermia therapy systems. In a range of award-winning German laboratories, Oncotherm Group scientists work closely with other scientists, aiming to produce new medical-technology findings that can enter into new and existing products. Overall, such efforts are oriented to the goal of ensuring that all of the company's products always reflect the state of the art. Their research findings also serve as the basis for scientific papers designed to bring the Oncothermia method to the attention of doctors, hospitals and universities.



Technical and scientific work at our Hungarian location, where engineers and scientists collaborate to produce the company's latest developments.

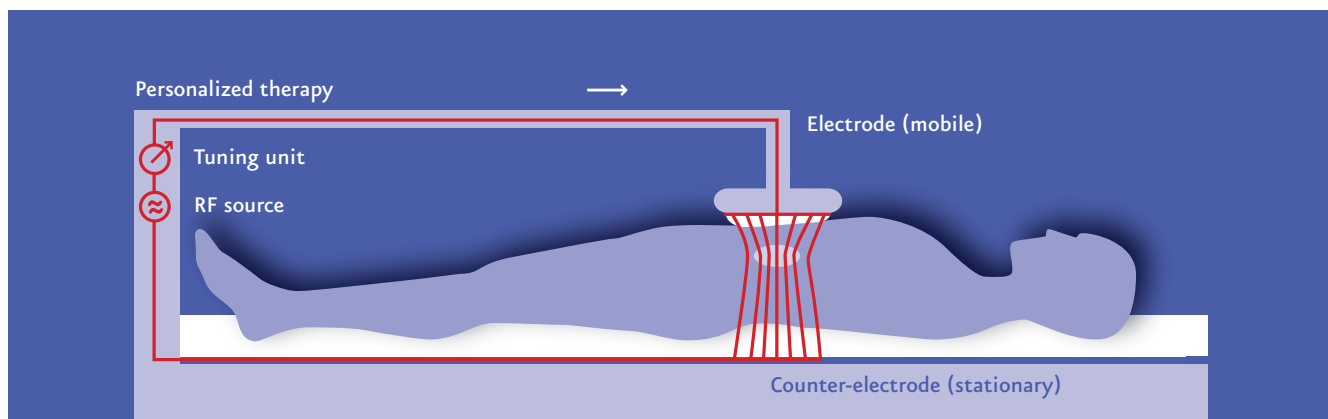
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How the method works and how it is used

Oncothermia is based on the classical method of Hyperthermia, one of the oldest cancer treatment methods. Unlike conventional Hyperthermia, however, Oncothermia does more than simply warm deep layers of tissue. It also combines such warming with a modulated electric field, with a carrier frequency of 13.56 MHz, that is generated by two active electrodes. A mobile electrode is positioned in accordance with the body area being treated, while a second, stationary electrode always remains in a fixed position below the patient, integrated within the therapy bed. Micro-biological tests have proven that malignant tissue has higher conductivity than healthy human tissue. As a result, the electric field tends to flow predominantly through the malignant tumor tissue. This effect is referred to as “selection at the cellular level”. The combination of deep-layer heating and the electric field leads to stimulation of malignant tumor cells. This, in turn, inhibits the natural activity of malignant cells and triggers and supports the body’s immune response. Malignant tumor cells then die via a process known as “apoptosis”. Oncothermia treatment thus is based on two key effects: energy absorption and cellular-level selection.

Oncothermia: the method



Schematic illustration of Oncothermia treatment: The illustration shows how the electric field, produced by the two active electrodes, passes through the patient’s body. As shown schematically, the electric field tends to move through the pathways with the lowest impedance, i.e. through the malignant tissue (tumor).

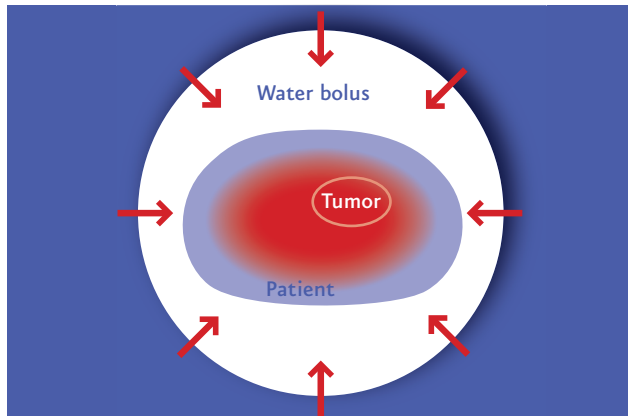
Additional information on conductivity

Malignant cells are individual, autonomous cells, and they have a higher metabolic rate than neighboring healthy cells. This difference facilitates selection of malignant cells even in highly mixed tissue containing large numbers of healthy and malignant cells. Such selection is enhanced by the electric-field modulation, which can reveal the irregular, non-collective behavior of individual malignant cells. This effect of modulation is unique and exclusive to Oncothermia therapy.

Hyperthermia and Oncothermia – explaining the difference

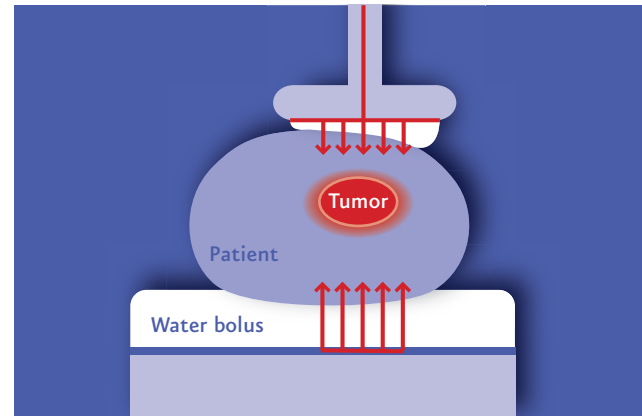
Oncothermia, a unique improvement on conventional oncological Hyperthermia, represents the next generation of Hyperthermia therapy. It selectively destroys malignant cells by applying the required specific energy dose. While traditional Hyperthermia functions solely via certain thermodynamic parameters, such as temperature, Oncothermia functions by controlling absorbed energy doses, via an approach similar to that used in radiation therapy. Oncothermia moves beyond conventional heat therapies by using controlled, selective energy transfer. Oncothermia transports energy directly to malignant cells, via a selecting electric field. The therapy thus functions in a largely apoptotic manner. The entire treatment is controlled by the modulated electric field that passes through the patient. In the process, the tumor becomes a constant, controllable parameter within a closed electric circuit.

Hyperthermia: even, focused heating



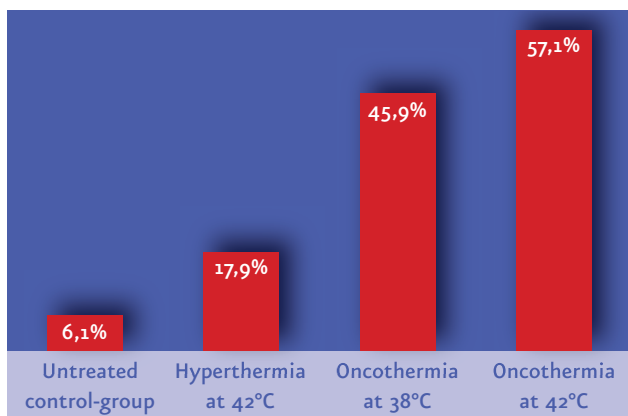
Both malignant and healthy tissues are uniformly heated from all sides. The temperature difference between tumor cells and surrounding healthy tissue is hardly measurable (even, focused heating).

Oncothermia: conductive heating



The electric field and resulting heat are directed to the area of the tumor cells, so the temperature of the healthy tissue increases only very slightly (conductive heating).

Percentage distribution of killed cells after Hyperthermia and Oncothermia treatment

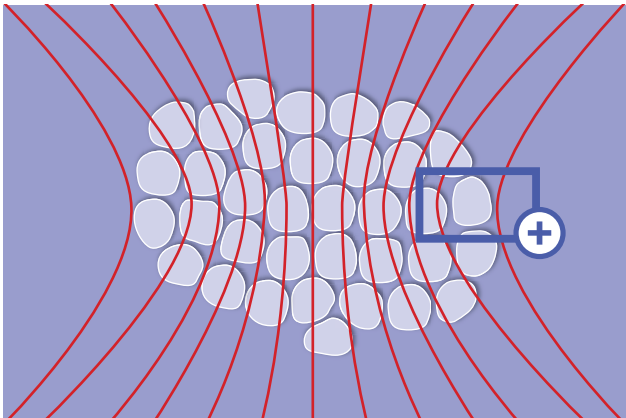


Already at a temperature of 38°C, Oncothermia therapy yields better results than classic Hyperthermia does even at a higher temperature of 42°C. The number of killed cells is 2.5 times higher.

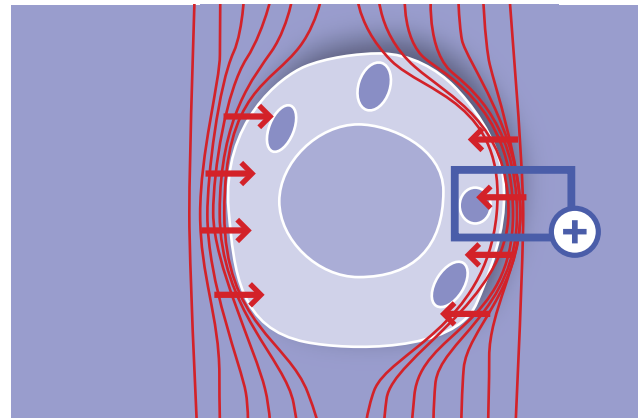
Effects at the cellular level

Oncothermia selects at the cellular level. A number of cell-culture experiments have shown that Oncothermia has almost no impact on healthy cells; benign cell cultures with high proliferation were found to be slightly affected. Malignant cells in cell cultures, however, are selectively destroyed by Oncothermia. (Source: Dr. G. Brunner, Klinikum Hornheide, Clinic of Münster University, Hyperthermia Symposium 2006, Cologne). The selection occurs as a result of special metabolic characteristics of malignant cells (incidentally, this can also be proven by positron emission tomography). The special feature of Oncothermia is that it promotes renewed formation of cell connections (E-cadherin and -catenin junctions), thereby facilitating the natural cell-death process (apoptosis). Cell scattering is reduced, and apoptosis is initiated via delocalization of β -catenin and activation of the tumor-suppressor protein p53.

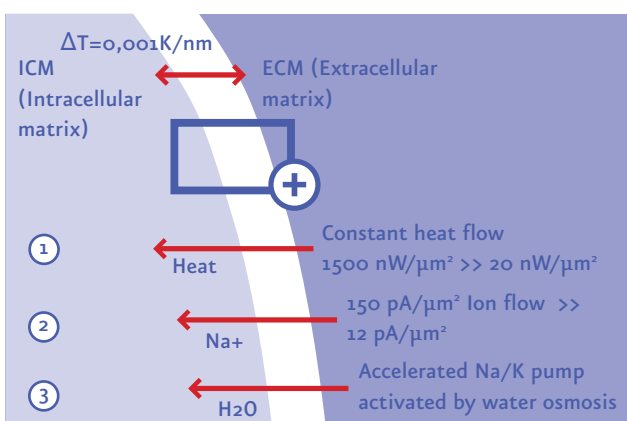
Schematic illustration of the detailed processes in the cell



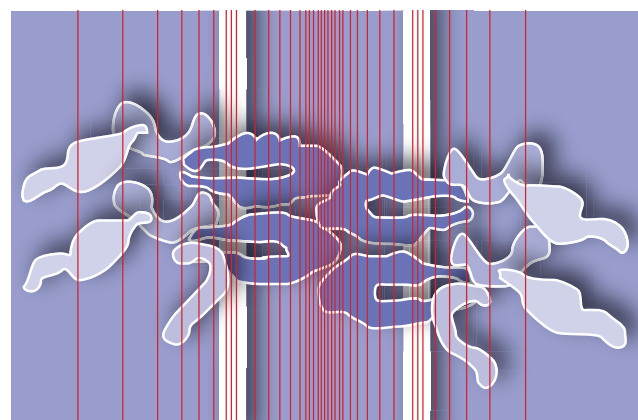
1. Illustration of individual tumor cells within the modulated electric field, showing how the electric field focuses on the tumor cells.



2. Illustration of the electric field along the membrane of a malignant cell. Here, the electric field is beginning to affect the biochemical processes of the cell membrane.



3. Detail of a malignant cell with cell membrane and intracellular and extracellular domains. The electric field has changed the membrane's potential, thereby initiating various reactions within the intracellular and extracellular domains, such as increased intracellular sodium concentration within the cell and an efflux of potassium.

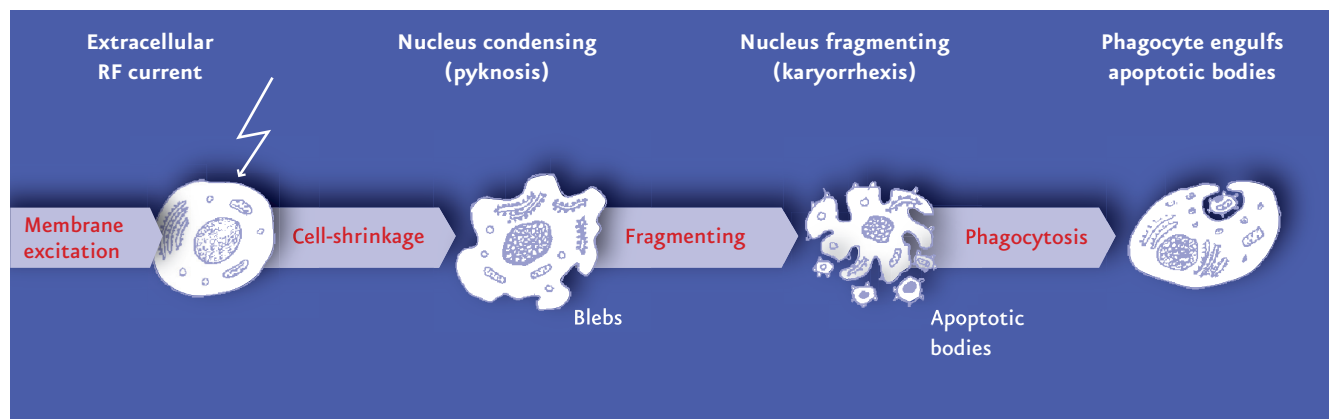


4. Detail of a malignant cell membrane. As a result of the change in the membrane potential, previously severed cadherins within the cell membrane reconnect, and the membrane's permeability and interaction between the intracellular and extracellular domains are restored.

Apoptosis induced by Oncothermia

Hyperthermia treatment kills malignant cells largely via necrosis. In the process, toxins are released that can burden the immune system. Oncothermia, on the other hand, harnesses the immune system to induce apoptotic death of malignant cells. Apoptosis pathways can be triggered and measured via β -catenin and connexin. Apoptosis can even be retraced morphologically, although β -catenin is the most efficient indicator for demonstrating natural apoptotic change after 72 h (see illustration).

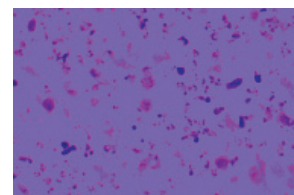
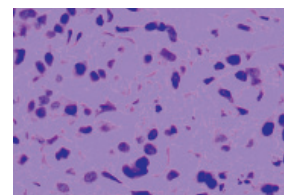
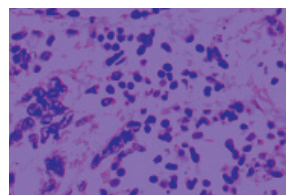
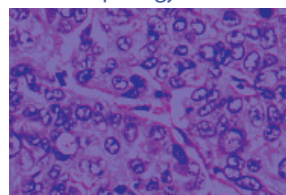
The process of apoptosis induced by Oncothermia treatment



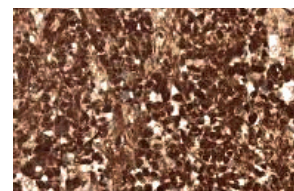
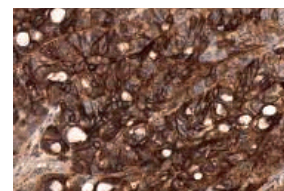
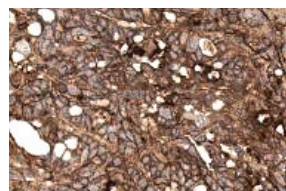
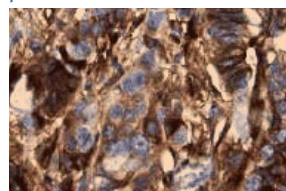
Time after treatment



Mikromorphology



β -catenin

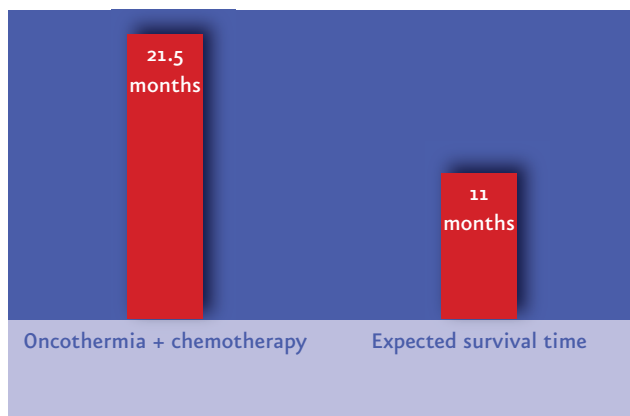


Oncothermia treatment initiates the process of apoptosis, the programmed death of malignant cells, which can be divided into 4 different chronological phases. During the first phase of apoptosis, about 1/2 hour after treatment, the cell starts to shrink; during the second phase (after about 8 hours) the nucleus condenses and cell membrane deformation starts; during the third phase (about 24 hours after treatment) the nucleus slowly begins to dissolve and fragments (apoptotic bodies) detach from the cell membrane; in the last phase of apoptosis (about 72 hours after treatment), such fragments are engulfed by phagocytes.

Synergy in a combination with conventional tumor therapies

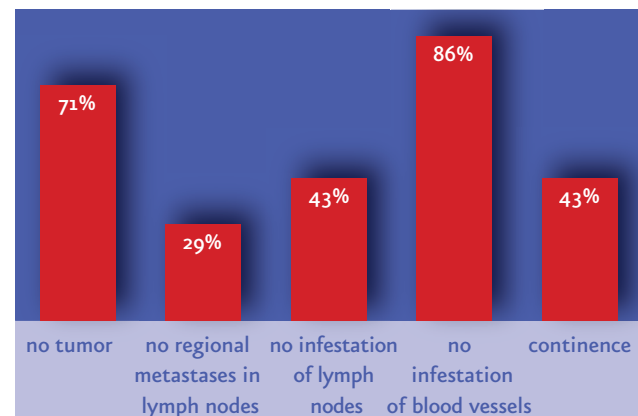
Treatment is always focused on the specific patient involved, meaning that the method and the electric field are specifically adjusted to the patient. Oncothermia supports natural processes of the human body (including apoptosis, immune system response ...). It is complementary to accepted conventional oncological treatment methods, it can be combined with all types of chemotherapy and radiation therapy and it can support the pre- and post-operative phases of surgical treatment. Oncothermia presents no risks for the patient. On the contrary: patients tend to find the treatment even pleasant. Oncothermia is not intended to serve as a sole cancer therapy, however. It is closely oriented to conventional medical treatment and should be used in a supporting role with such treatment. Studies have shown that a combination of Oncothermia and radiation or chemotherapy can be highly effective, and that Oncothermia strongly enhances the effects of such other treatments. Oncothermia markedly improves patients' quality of life and their chances for a complete cure.

Oncothermia in combination with mytomycin-C



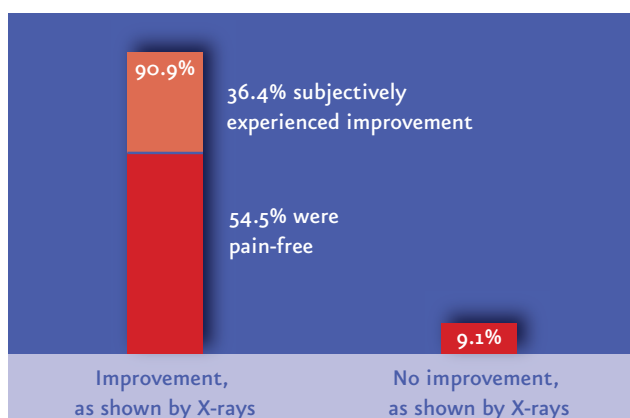
A combination of Oncothermia treatments and mytomycin-C chemotherapy can sharply increase cell-death rates, by up to 66.1%. This implies that Oncothermia boosts the effects of chemotherapy and can enhance the results obtained at the cellular level. While conventional Hyperthermia also improves the effects at the cellular level, its improvement rate, at 7.7%, is much lower than that provided by Oncothermia.

Oncothermia and surgery



Oncothermia treatment for patients with inoperable rectal carcinoma. After treatment, 71% of the patients were operable (Prof. H. Renner, Hyperthermia Symposium, Cologne, October 2003)

Oncothermia in combination with radiation therapy



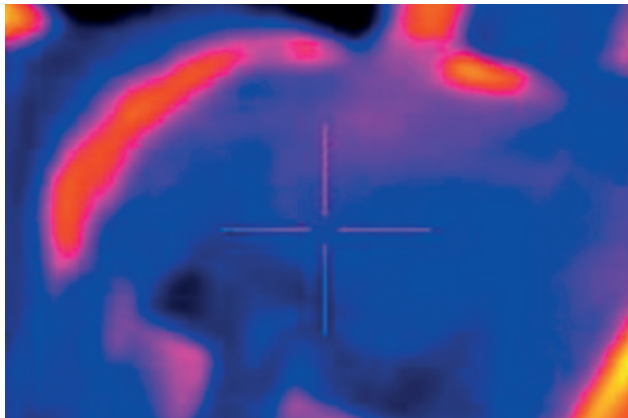
Depending on the tumor's blood-perfusion status, Oncothermia treatment is applied either prior to or after the ionizing radiation. With low blood perfusion, the aim is to increase the oxygen content of the blood, to support the therapy's ionization effect. That end calls for the Oncothermia treatment to use a low energy dose. In case of high blood perfusion, radiation is normally expected to be highly effective. For best results, Oncothermia treatments following radiation must provide the maximum possible (tolerable) energy dose.

TÜV-certified patient and user safety

Oncothermia is safe, for both patients and users. When the electric field is precisely focused on the malignant tissue, low energy levels can be used. Thanks to efficient energy absorption, the targeted treatment does not overheat the skin, even at low cooling settings, and the patient feels comfortable throughout the treatment.

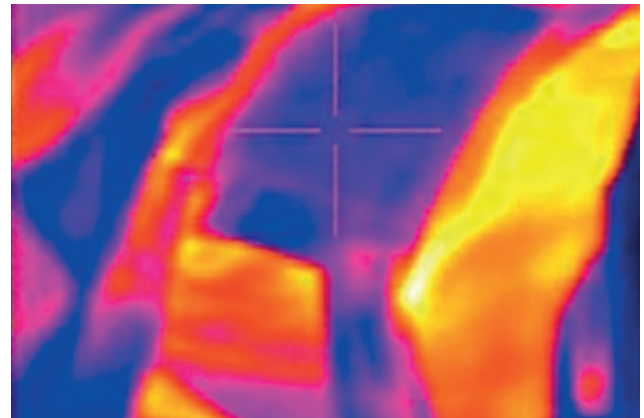
Since treatment is restricted to the tumor region, the patient does not have to worry that other body regions will be affected. Due to the selection at the cellular level, the electric field only acts on the tumor area without harming adjacent healthy cells in the process.

Multi-local Oncothermia treatment (with a large textile electrode) – Thermal image after 60 minutes of treatment



The electrode hardly heats up at all. The heat is produced in deep layers of the body, not on its surface, and thus cannot burn the patient's skin.

Local Oncothermia treatment (with a small textile electrode) – Thermal image after 60 minutes of treatment



In local Oncothermia treatment as well, very little heat is generated in the vicinity of the electrode. The patient's safety is guaranteed; there is no risk of skin burns.

Needless to say, all electromagnetic radiation devices used for tumor treatment must fulfill stringent safety requirements. We meet such safety requirements via our own high standards and solid scientific findings, and via the low levels of radiation that our devices produce. With sophisticated tuning systems and specially designed electrodes, our devices can precisely focus energy within patients, without exposing the environment to radiation. Our systems conform to requirements for electromagnetic compatibility Class B, which means that they may even be used in residential areas. As a result, not only the patient is safe, the system operator and the medical staff who work long hours near the system, on a daily basis, are safe as well.

Oncotherm systems have been tested by TÜV Productservice Munich and legally certified. With more than 100,000 treatments per year, the Oncothermia method has proven itself in actual practice.

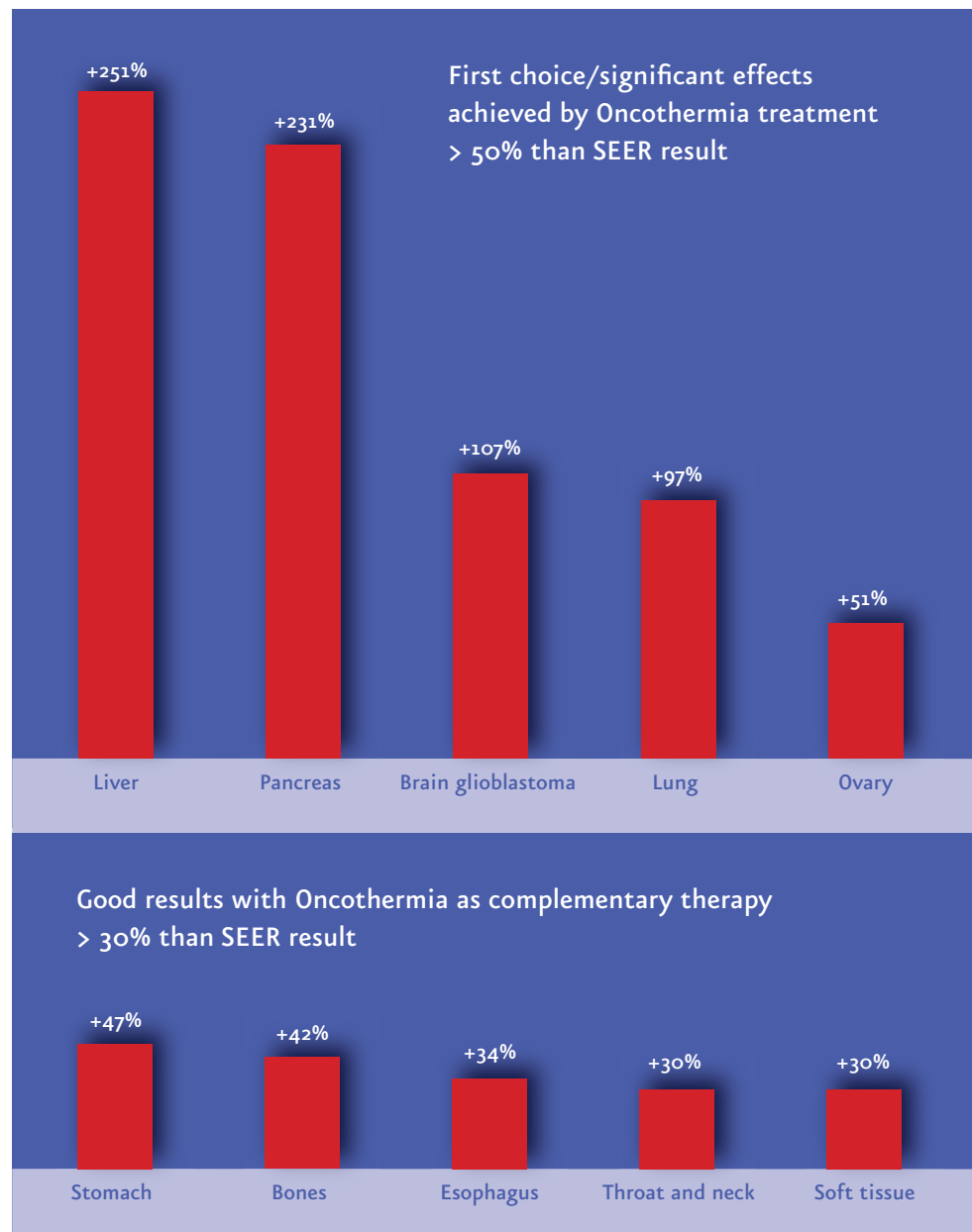


Medical and therapeutic benefits

Oncothermia, when used as a complementary treatment along with traditional medical therapies such as chemotherapy and radiation therapy, can significantly improve patients' conditions, prolong their survival and enhance their quality of life. This claim is backed by numerous case studies provided by leading doctors, both in Germany and in other countries, who use Oncothermia therapy on a daily basis in their offices and clinics. With their combination of electric field and heat, Oncotherm systems can also be used for the treatment of parts of the human body that are in constant motion, such as the lung, and of heat-sensitive regions, such as the brain. They are effective in body regions with high levels of blood flow, such as the liver, and in regions with high levels of air circulation, such as the lung. Many such body regions cannot be treated with other methods that are based on conventional Hyperthermia, since such methods use temperatures over 40°C. In general, Oncothermia can be used with all stages of cancer, although its current main use is with advanced solid tumors that are hardly operable or inoperable, as well as with recurrent tumors and metastases.

Additional average survival time after Oncothermia treatment, compared to SEER database

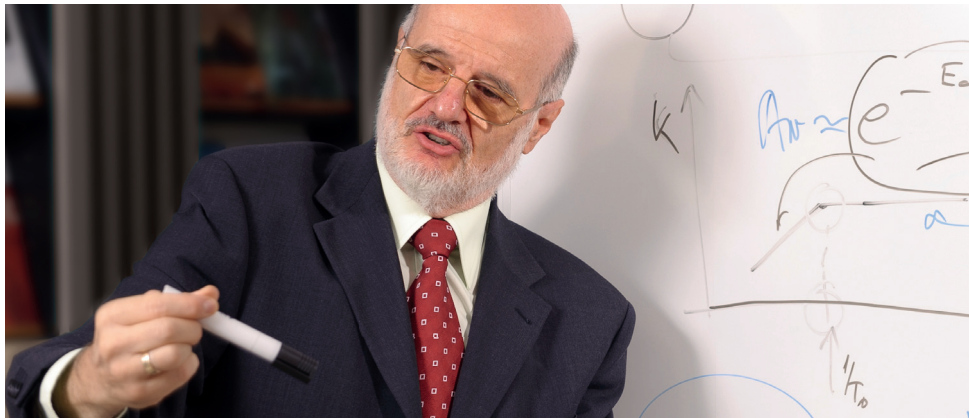
Results and numbers of cases from a large-scale retrospective study on the use of Oncothermia on different tumor entities. For all tumor entities studied, studied patients showed a higher survival rate in the first year after cancer diagnosis.



Oncothermia has already been successfully used with the following tumors, including their metastases in different organs:

- | | | |
|----------------------------------|-----------------------------|---|
| - Astrocytomas and glioblastomas | - Hepatocellular carcinomas | - Ovarian carcinomas |
| - Bronchial carcinomas | - Stomach carcinomas | - Pancreatic carcinomas |
| - Cervix carcinomas | - Malignant melanomas | - Squamous epithelium carcinomas at head and throat |
| - Colorectal carcinomas | - Mamma carcinomas | |
| - Carcinomas of the urethra | - Renal cell carcinomas | |
| | - Esophagus carcinomas | |

Where conventional therapy approaches (surgery, chemotherapy, radiation therapy) are not very likely to be successful, or have proven to be inadequate, Oncothermia may also be the choice for tumors not included above, especially if the aim of therapy is palliation.

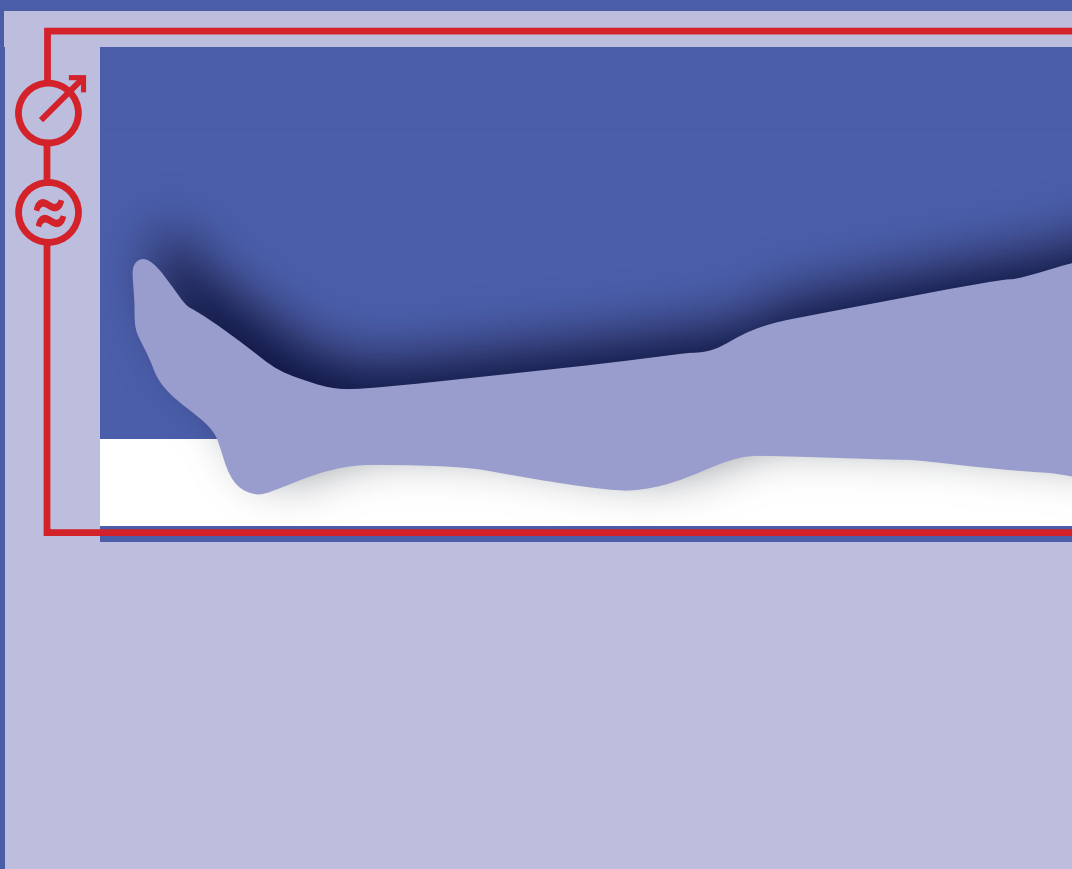


Plans for future research

Oncothermia is still far from having reached its full potential. Day in and day out, we gain new knowledge, from both medical practice and our own experiments, of relevance to improving the method. Wherever possible, the Oncotherm team applies such new knowledge, with a view to ensuring that our products are always state-of-the-art.

In the science sector, we are working especially hard to disseminate the theory and practice of Oncothermia throughout the world. Our scientific consultant, Prof. Dr. Szász, attends the world's leading medical conferences in the area of complementary medicine, and he presents the latest relevant research findings and progress achieved in improving our method. Every year, our qualified staff presents the new Oncotherm products at numerous trade fairs, both at home and abroad. Our most recent developments include medical devices for supporting chemotherapy, as well as new products for galvano therapy.

We are well aware of both the capabilities and the limits of traditional oncological treatments. We therefore strive continuously to improve the Oncothermia method, with a view to enhancing combined use of conventional methods and Oncothermia in connection with malignant tumors. Our efforts, both in thought and action, are aimed at supporting doctors and patients in their fight against cancer.



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