Introduction of Clinical Practice on Integrative Therapies During and After Women's Cancer Treatment Focusing on Hyperthermia

介紹以熱療為重點的婦女癌症治療期間和之後的綜合療法的臨床實踐

凌昌明醫師

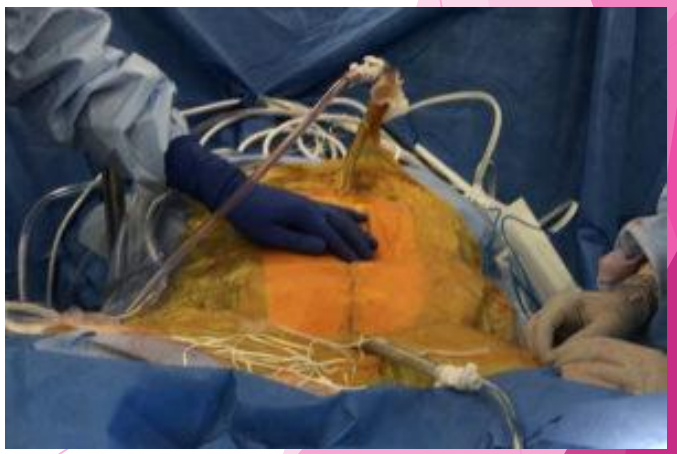
2020/09/04

Locoregional hyperthermia

- External hyperthermia
- Interstitial hyperthermia
- Endocavitary hyperthermia used for deep-body sites ie esophagus, rectum
- Hyperthermic Intraperitoneal Chemotherapy







Local hyperthermia (superficial, external, interstitial)

ICD-10 Procedure	
D0Y78ZZ	Hyperthermia of peripheral nerve
D7Y38ZZ	Hyperthermia of neck lymphatics
D7Y48ZZ	Hyperthermia of axillary lymphatics
D7Y88ZZ	Hyperthermia of inguinal lymphatics
DBY78ZZ	Hyperthermia of chest wall
DHY28ZZ	Hyperthermia of face skin
DHY38ZZ	Hyperthermia of neck skin
DHY48ZZ	Hyperthermia of arm skin
DHY68ZZ	Hyperthermia of chest skin
DHY78ZZ	Hyperthermia of back skin
DHY88ZZ	Hyperthermia of abdomen skin
DHY98ZZ	Hyperthermia of buttock skin
DHYB8ZZ	Hyperthermia of leg skin
DMY08ZZ	Hyperthermia of left breast
DMY18ZZ	Hyperthermia of right breast
DWY18ZZ	Hyperthermia of head and neck
DWY28ZZ	Hyperthermia of chest
DWY38ZZ	Hyperthermia of abdomen
DWY68ZZ	Hyperthermia of pelvic region

ICD-10 Diagnosis	
C00.0-C14.8	Malignant neoplasm of lip, oral cavity and pharynx
C43.0-C43.9	Malignant melanoma of skin
C4A.0-C4A.9	Merkel cell carcinoma
C44.00-C44.99	Other malignant neoplasm of skin
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C50.011-C50.929	Malignant neoplasm of breast
C76.1	Malignant neoplasm of thorax
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C79.2	Secondary malignant neoplasm of skin
C79.81	Secondary malignant neoplasm of breast
C79.89	Secondary malignant neoplasm of other specified sites [chest wall]
D03.0-D03.9	Melanoma in situ
D04.0-D04.9	Carcinoma in situ of skin
D09.8	Carcinoma in situ of other specified sites

Conditions Treated

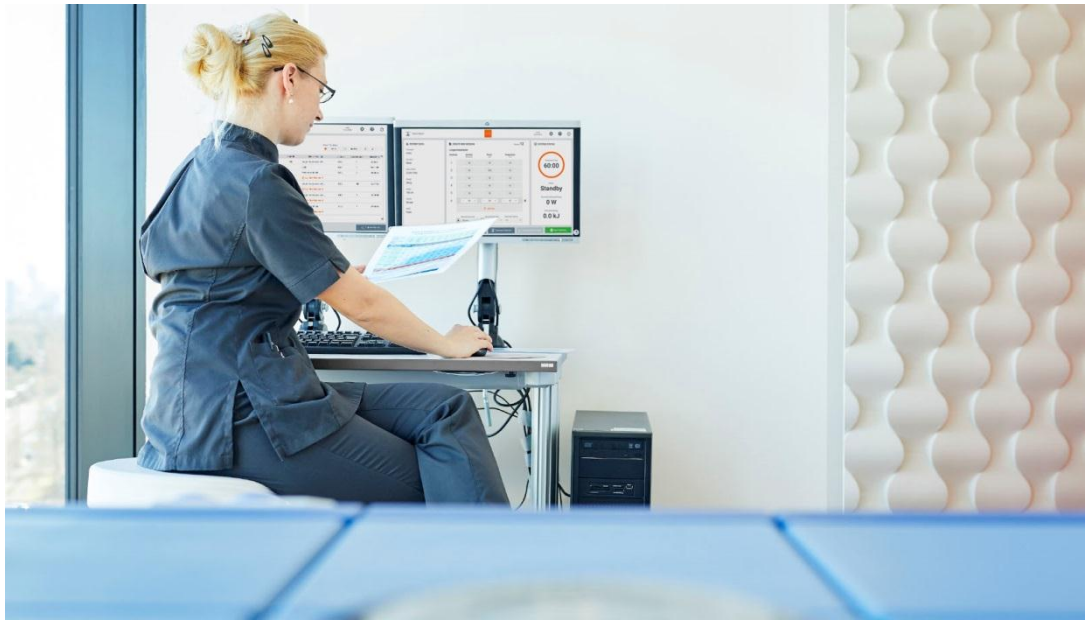
- Recurrent breast cancer
- Locally advanced breast tumors

To treat tumors that are close to the surface of the body. A special device called a surface applicator is applied over the region of the tumor. The tumor area is heated to a temperature of **40-43°C** (**104-109°F**) for approximately one hour. Hyperthermia treatments are given within one hour of radiation therapy or chemotherapy.

- There is a clear rationale for using **hyperthermia** in cancer treatment.
- Treatment at temperatures between 40 °C and 44 °C is cytotoxic for cells in an environment with a **low pO2** and **low pH**, conditions that are found specifically within tumour tissue, due to insufficient blood perfusion.
- Under such conditions radiotherapy is less effective, and systemically applied cytotoxic agents will reach such areas in lower concentrations than in well perfused areas. Therefore, the addition of hyperthermia to radiotherapy or chemotherapy will result in at least an additive effect.

The healing power of fever to fight cancer

- Local hyperthermia functions in the same way as a controlled, regionally restricted fever. Two non-invasive electrodes raise the temperature in the tumor regions. The electromagnetic waves generate a temperature above 40° Celsius by causing the water molecules in the body to vibrate and to heat up the tissue.





- Both capacitive and electromagnetic radiative hyperthermia systems are used for superficial heating.
- Commercially available capacitive systems are Thermotron RF8 (Yamamoto Vinita Co, Osaka, Japan), Oncotherm (Oncotherm Kft, Budapest, Hungary) and Celsius TCS (Celsius42 + GmbH, Cologne, Germany), operating at a frequency of **8** or **13.56 MHz**.
- Radiative antennas induce an electromagnetic field that is coupled into the patient using a water bolus. Examples of commercial radiative superficial systems are the BSD-500 system (Pyrexar Medical, Salt Lake City, UT), the ALBA ON4000 (ALBA Hyperthermia, Rome, Italy) and contact flexible microwave applicators (CFMA) (SRPC Istok, Fryazino, Moscow region, Russia). These radiative systems have an operating frequency of **434** or **915 MHz** and are positioned contacting the treatment area.

Heating quality

- The frequent clinical application of two distinctly different techniques raises the question whether there are differences in heating characteristics between capacitive and radiative systems that lead to clinically relevant differences in heating quality.
- Treatment planning is a very useful method to analyze the differences between different heating techniques, using numerical simulation of power and temperature distributions

- Simulations for this study were performed using our in-house developed hyperthermia treatment planning software, which uses voxel-based finite difference calculations. The resolution applied for all simulations was $1 \times 1 \times 1\ mm^3$. The computational volume for the radiative heating was $269 \times 269 \times 159$ voxels; for the capacitive system dimensions were $319 \times 319 \times 289$ voxels. The definitions of the radiative applicator, electrodes and water boluses were generated using the Generic Object Format.

Contact Flexible Microstrip Applicators

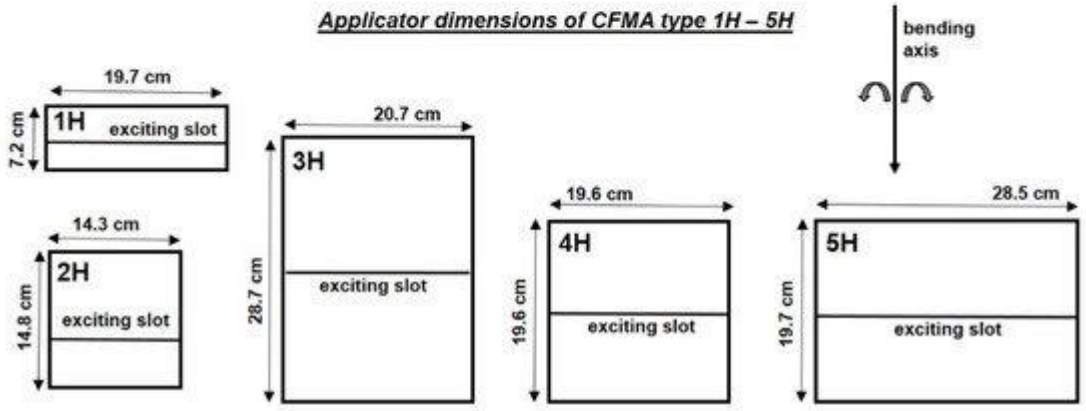
Photograph of CFMAs



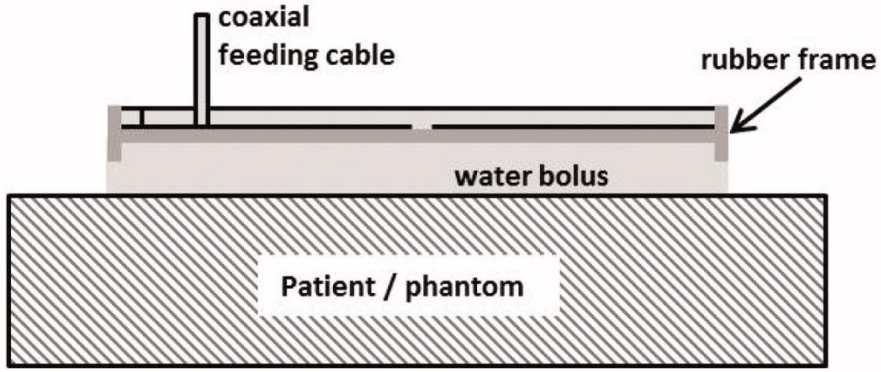
Photograph during treatment



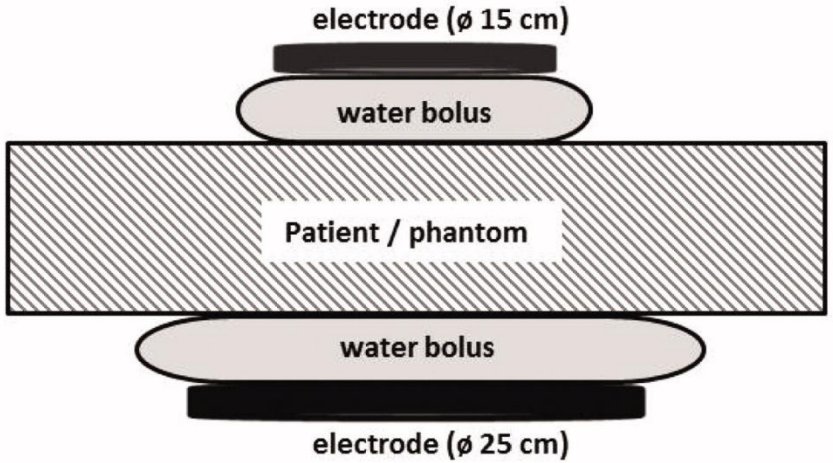
Applicator dimensions of CFMA type 1H – 5H



Front view CFMA

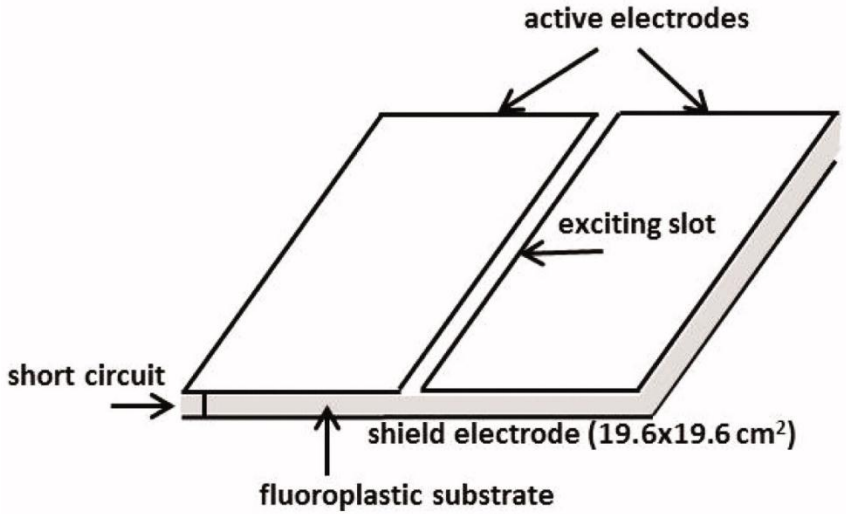


Front view capacitive system



CFMA electrodes

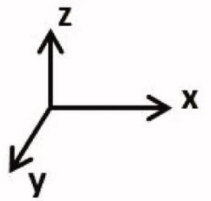
NB: upside-down
for visualization

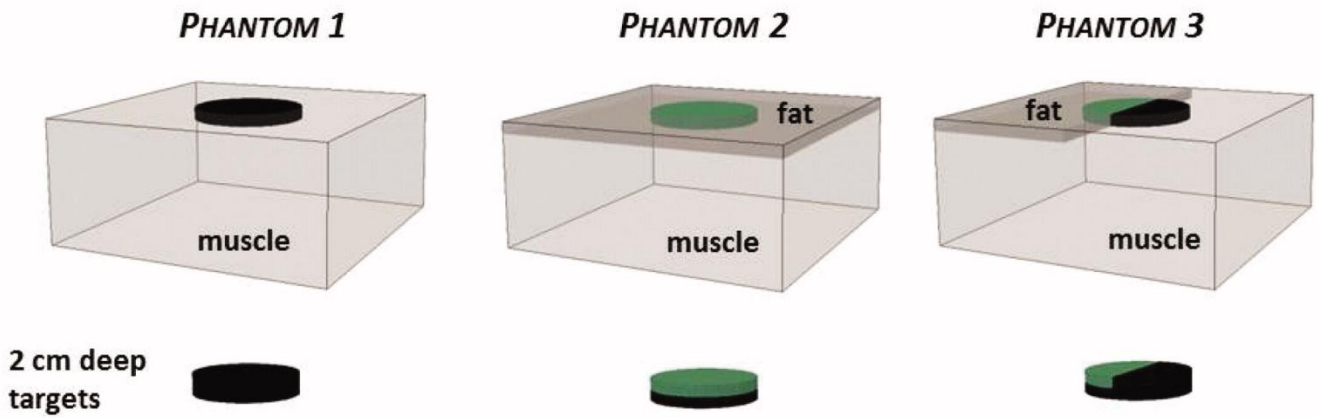


Phantom models

Target: cylinder, 10 cm diameter;
muscle-like (black), fatty (green)
1 cm deep (top row) and 2 cm deep (bottom row)

Fat layer: thickness 1 cm





Integrative oncology

- It refers to the use of complementary and integrative therapies in collaboration with conventional oncology care.
- Enhancing wellness, improving **quality of life (QOL)**, and relieving symptoms of disease and side effects of conventional treatments.

The body’s natural intelligence

- In the presence of higher temperatures, the organism accelerates its biochemical processes and boosts the immune response. Very gently. In harmony with nature.
  Tumor cells are sensitive when it comes to heat. They respond with heat shock proteins, i.e. protein substances that call on the immune system’s killer cells to attack the tumor as soon as they reach the cell membrane.
  The immune system appears to have a memory that retains the appearance of the tumor. Current hypotheses presume that this immune cell memory helps to prevent new metastases. Perfect synergy.

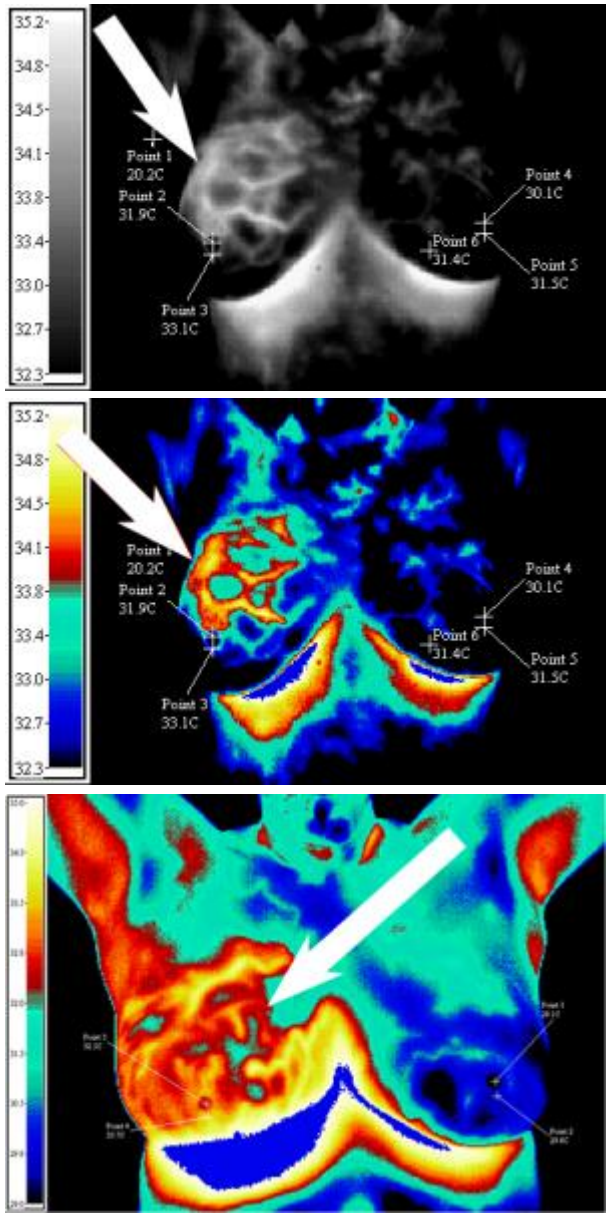
- Hyperthermia therapy is of particular use in cases where circulation and oxygenation in the tumor tissue already are poor, i.e. in the presence of hypoxia. Or in cases where the radiation treatment needs an effective amplifier because it has to be administered in low doses to protect the surrounding tissue.



- Even in cases of relapse, hyperthermia is a helpful and considerate partner because the previously radiated body areas have already been affected.
- A growing number of studies and research projects on hyperthermia have been initiated in past years. The results have been promising. Oncologists and radiologists quite naturally make greater use of hyperthermia as a complementary and relevant component in the cancer treatment canon. Natural healing. Gentle and effective.

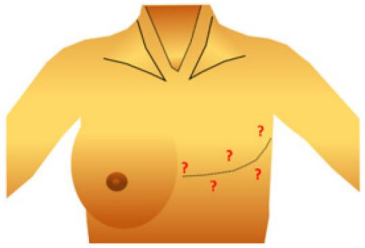
Breast Thermography

- **Increased metabolism.** (Lawson 1956, 57 and Amalrie 1957, Lawson and Chughtai 1963 (3)
- **Hypervascularity,** including angiogenesis and release of angiogenic factors. (Lawson 1956, 57 and Amalrie 1957, and Chughtai 1963)
- **Thermoregulatory Dysfunction ,** including the presence of nitric oxide (6, 7, 8) and “host immune response” (11). (Chapman 1989, Head, Elliott 1993, Ambar 1994)



Inflammatory Breast Cancer (IBC)

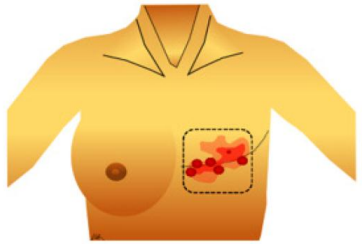
- Increased skin temperature noted with cancerous breasts may be due to **enhanced blood flow** from the core temperature through the affected breast.
- Increased blood flow can be a result of **hypervascularization associated with the new blood vessel growth** as a result of the malignancy or enhanced blood flow through existent microvascular structures







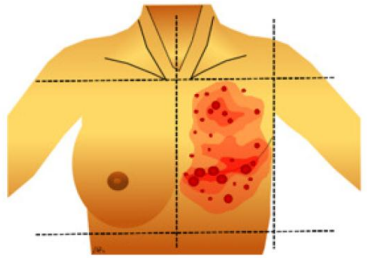
rClass 0:
microscopic disease







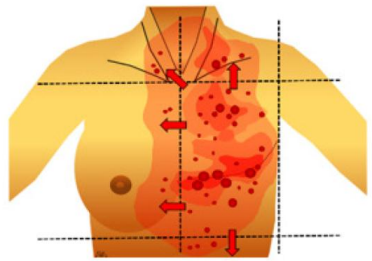
rClass I:
ipsilateral chest wall, max. diameter ≤ 10 cm or continuous tumor area ≤ 100 cm²







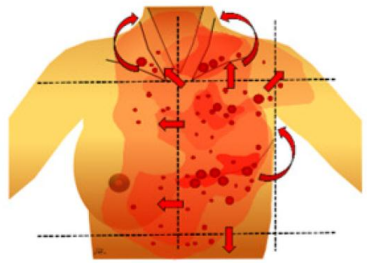
rClass II:
ipsilateral chest wall, > 100 cm², not surpassing midsternal and midaxillary line, clavicle and lower costal margin







rClass III:
chest wall and supraclavicular fossa and/or contralateral chest wall or breast and/or abdominal wall







rClass IV:
rClass III + extensions on the back (cancer en cuirasse)

Evaluation of Therapeutic Outcome Based on a Novel Size Classification
Markus Notter, *Cancers* **2020**, *12*(3), 606;

Treatment response of a patient with LRBC, rClass III

(A)



(A) April 17, 2018: extended locally recurrent breast cancer patient before retreatment (rClass III, 2 treatment fields)

(B)



(B) November 12, 2018: after 2 series of HT/RT, 5 × 4 Gy, 1×/week

Treatment response of a patient with LRBC, rClass IV

(A)



(B)



(C)



(D)



(A) July 10, 2018: patient with very extended locally recurrent breast cancer “cancer en cuirasse”, rClass IV, before combined treatment of the anterior chest wall.
(B) November 12, 2018: 2 months after HT/RT, 5 × 4 Gy 1×/week.

(C) August 20, 2018: same patient: tumor situation on her back/right shoulder just before combined treatment.
(D) November 12, 2018: 3 weeks after after

Evaluation of Therapeutic Outcome Based on a Novel Size Classification

- The hypofractionated treatment schedule and heating technique described in this analysis leads to satisfying responses and local control rates. Treatment-related toxicity, especially acute and chronic skin damage, could be significantly reduced compared to other schedules and techniques described before.

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- The novel classification presented here is well feasible in the analysis of patients with pre-irradiated LRBC and allows for the assessment of chances and limitations of combined HT/re-RT in the treatment of different tumor sizes. It may improve comparability of data and stratification of prognostic groups, thus helping to guide the decision between curative and palliative intent. Using this classification, the retrospective analysis of 201 patients treated with **contact-free, thermography-controlled wIRA-HT** immediately followed by **hypofractionated re-RT (5 × 4 Gy, 1×/week)** results in a high clinical overall response rate and a satisfying local control rate even in large-sized tumors of LRBC. Low toxicity allows for repeated re-irradiations in case of re-recurrences.

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Whole body hyperthermia (WBH)

- Whole body hyperthermia (WBH) uses either radiation heat or extracorporeal technologies to raise the temperature of the whole body to at least 41 °C. The typical method used for WBH is immersion in a hot water bath and radiant heat with ultraviolet radiation. In radiant WBH, heat is superficially applied to the whole body using hot blankets, inductive loops, or thermal chambers.

- Depending on the type of WBH, patients may request **general anesthesia** or **deep sedation** during treatment. Heating the body up to 42.0 °C for 60 minutes (dangerous WBH) or 39.5–41.0 °C for three to four hours (modest WBH) may otherwise become difficult. A WBH treatment session usually continues for four hours. It takes **two hours** to reach the target temperature, which is maintained for a further **one hour** and is followed by a **one hour cooling period**. To preserve the patient's systolic blood pressure above 100 mmHg, normal saline is injected. The patient is then checked weekly for problem issues.

Oman Med J. 2016 Mar; 31(2): 89–97.

- While WBH can present the most homogeneous thermal supply, this is associated with the highest chance of difficulties (e.g., **thermal pressure in the heart, lungs, liver or brain**). **Diarrhea, nausea, and vomiting** are frequently seen, but they are temporary side effects.

Oman Med J. 2016 Mar; 31(2): 89–97.

- In carcinomas with **distant metastases**, a fixed maximum temperatures of **42 °C** can be preserved for one hour with minor adverse results. Such a procedure can be achieved only in **deep numbness and calm, or general anesthesia**. Whether intubation is essential for safe administration is still under debate.

Oman Med J. 2016 Mar; 31(2): 89–97.

Instruments used in hyperthermia treatments

- Microwaves (433 to 2450 MHz), radio waves (100 KHz to 150 MHz), ultrasound, hot water perfusion (e.g., the use of tubes and blankets), resisting wire embeds, ferromagnetic seeds, nanoparticles, and infrared radiators are used to apply heat to tumors.

23rd ESHO Meeting Berlin; 2006

- Two kinds of probes are used in HT. One to transmit energy to the tissue, an applicator, and another to screen the tissue temperature. Every applicator contains a bolus on the patient's skin. At the time of treatment, this bolus is filled with flowing water that can be heated as required. The bolus helps to physically connect the electromagnetic waves to the patient's body, and decrease the reflection and loss of energy. Heat can then be applied with interstitial and intracavitary probes or external antennas.

- Radio frequency at 8–12 MHz is beneficial for heating dee*p*-seated tumors whereas microwave heating at 434–915 MHz is beneficial for superficial tumors. Heating with ultrasound is also possible. Mechanical ultrasonic waves (at 0.2–5 MHz) can efficiently heat a small volume at different depths. Unlike ultrasound imaging, using ultrasonic waves as a heating source has not been utilized clinically

Novel Beyond Conventional Approaches. Istanbul: InTech Open Access Publisher; 2011. p. 455-475

- The efficiency of HT is related to the temperature achieved during the treatment, as well as the length of treatment and tissue features. To confirm that the required temperature is obtained, but not surpassed, **the temperature of the tumor and adjacent tissues is checked** during the procedure.

- Another challenge of HT is to minimize the damage to healthy tissue. To do this, the aim is to preserve **local temperatures under 44 °C** and to preserve the **whole body temperature under 42 °C**, which is the maximum temperature the human body can tolerate.

Using magnetic nanoparticles to increase treatment effects

- Metastatic and locally advanced disease stages are not suitable for surgical resection, and most of the patients who undergo surgery relapse. A new approach to thermal treatment uses magnetic nanoparticles (MNP) in combination with heat. In this technique, **iron oxide nanoparticles** are infused into the target tissue, and **a magnetic field** is used for heating. This offers a chance to heat tumors located in deep body sections like skull (to treat frequent glioblastoma) or the pelvis (for treating prostate and cervical carcinoma).

23rd ESHO Meeting Berlin; 2006

- Homogenous delivery of heat depends on various factors such as the **tumor size** and **depth**. The development of this method may overcome the prior restrictions related to older HT techniques, like the inability to target heat to the tumor, homogenous heat distribution at every point of the entire tumor, and inherent problems with targeting indiscernible micrometastases (微轉移), which cause reduced disease and death for patients.

Ito A, Tanaka K, Honda H, Abe S, Yamaguchi H, Kobayashi T
J Biosci Bioeng. 2003; 96(4):364-9

Combining hyperthermia and other treatment strategies

- HT is **rarely used as a sole cancer treatment method** and is typically added to different cancer treatments. For various combinations of treatment, research and clinical trials have been conducted concentrating on the treatment of many kinds of cancers, mainly those with poor treatment results (e.g., melanoma, soft tissue sarcoma, malignancies of the brain, head and neck cancers, lung, breast, esophagus, cervix, colon, bladder, and liver). Some methods have verified the effectiveness of HT in combined treatment.

Lancet Oncol. 2002 Aug; 3(8):487-97.
Ann Oncol. 2002 Aug; 13(8):1173-84.
Crit Rev Oncol Hematol. 2002 Jul;

- In general, thermal side effects are transient. Since phase III clinical trials have shown benefits of combined HT and radiotherapy regimens for numerous malignancies, it is important to recognize the mechanism that leads to improved tumor cell death.

Lancet. 2000 Apr 1; 355(9210):1119-25
J Magn Magn Mater 1999;201(1):420-42

- The clinical reports have shown that chemotherapy achieves promising results in patients with body temperatures near 39 °C. The local or systemic temperature rises related to HT may enhance the sensitivity of cancer cells to chemotherapeutic drugs, boosting immunity and quickening apoptosis of tumor cells.
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Cancer Chemother Pharmacol. 2009 Nov; 64(6):1079-83.
Immunol Res. 2010 Mar; 46(1-3):137-54.

- The medical use of systemic HT 39–41 °C as an adjuvant to radiotherapy and chemotherapy is possible and produces beneficial therapeutic anticancer effects. Mild HT and chemotherapeutic agents have synergistic antitumor effects that increase the cytotoxicity of these drugs to cancer cells.

Eur J Cancer. 2001 Sep; 37(13):1609-16.

- It is believed that most alkylating agents and platinum agents have supra-additive cytotoxic effect when temperatures are increased from 37 °C to above 40.5 °C. An additional set of drugs, thermosensitizers, has a cytotoxic effect when applied in high temperatures. Some familiar drugs like **lidocaine** or **amphotericin B** have been proven to perform as thermosensitizers.
- HT combined with chemotherapy can increase the cytotoxicity of some chemotherapy drugs, such as cisplatin. *In vitro* studies reported that the anti-cancer effect of chemotherapeutic agents can be enhanced 10 to 100 times after heating at 42 °C.

Oncol Res Treat 1999;22(5):374-381

- Similarly, in palliative situations and recurrent cancer, HT was shown to preserve local progression free survival when joined with radiochemotherapy. The **synergic effect of heat and radiation relies on the time interval** between the two treatments, the temperature used, and the treatment order. When the two methods are implemented concurrently, the response is greater, and this method is preferable.

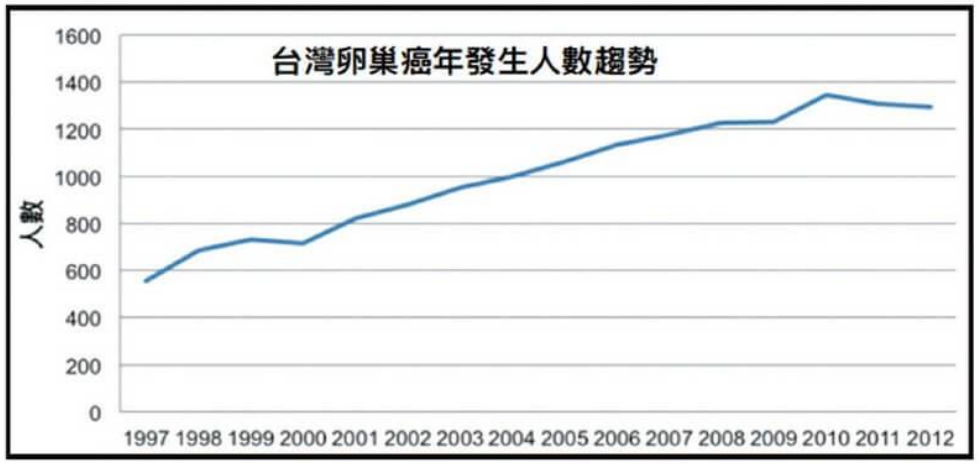
Radiother Oncol. 2010 Dec; 97(3):535-40.

- Local and regional HT approaches may offer greater therapeutic advantages than WBH. In several situations, the application of HT with different schedules of radiotherapy is advantageous. Improvements are still necessary for local and regional HT procedures.
- The clinical practice of using local and regional applicators needs development. **Better temperature control** may be obtained by using magnetic resonance tomography (MRT) combined with HT control methods

Lancet. 2000 Apr 1; 355(9210):1119-25.

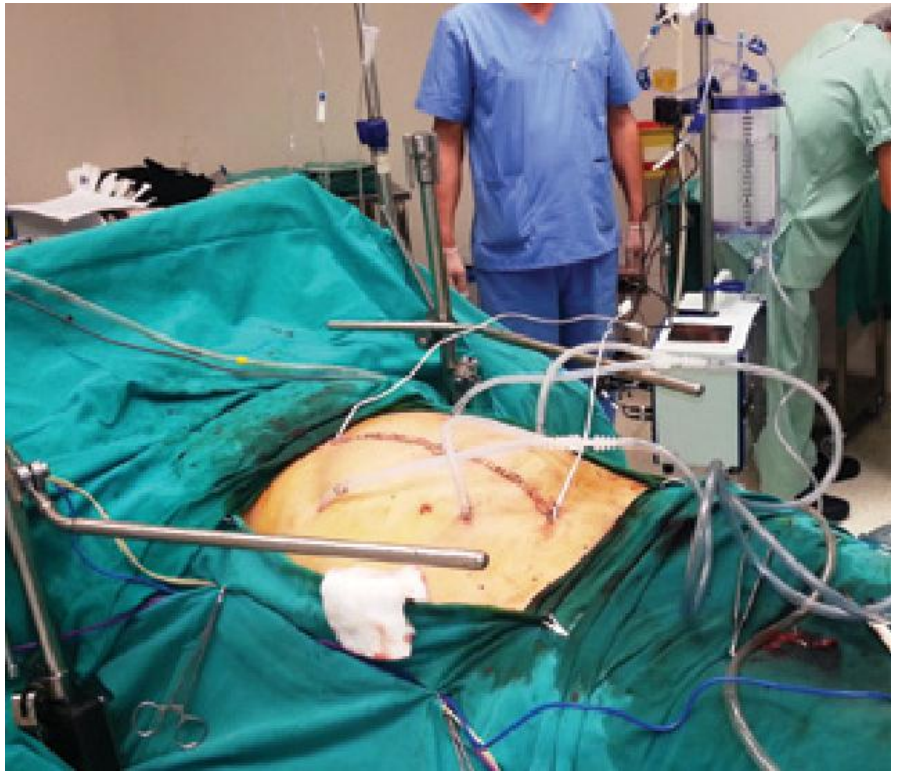
Ovarian cancers

- 女性卵巢癌在全球的發生率位居**第七位**，每年約19萬名新個案；在台灣，卵巢癌的發生率節節上升，十五年內**增加了二倍**以上，**每年有1300名新個案**。卵巢癌的五年死亡率高達60%，**位居台灣女性癌症死亡率的第五位**，為婦科癌症的頭號殺手，每年有548人（全球有11萬4千人）死於此病。近十年（2006～2016）台灣各重大癌症的死亡率多有改善或持平，唯獨卵巢癌的死亡率增加了29%，為增幅最大的癌症（圖一）；2016年起超越了子宮頸癌，名列男女十大癌症死因之一。



Hyperthermic Intraperitoneal Chemotherapy in Advanced Ovarian Cancer

- Hyperthermia as a new cancer treatment, promotes the greater omentum to absorb drugs, improves the utilization rate of chemotherapy drugs. Moreover, it can effectively kill cancer cells.





Open Med. 2018; 13: 83-89

- HIPC duration ranged from 30 to 120 minutes at a temperature between **39°C and 48°C**.
- Mean duration of the combined procedure, where reported, was **4.9 to 10.5 hours**. Where reported, HIPEC regimens included between one and four different drugs at varying doses. Mean number of procedures on each patient varied: 1.2 to 6.4 peritonectomies; 0.6 to 1.2 anastomoses; and 0.9 to 3.0 resections.
- The review indicated that HIPEC-based regimens was correlated with **better clinical prognosis** for patients with primary ovarian cancers.
- For recurrent ovarian cancers, HIPEC only improved the OS but did not elicit significant value on the PFS.

Fatigue comes with treatment

- Fatigue is an integrated phenomenon, and psychological factors, including the anticipation of fatigue, should not be neglected and the interaction between central and peripheral physiological factors also needs to be considered.
- Thermal therapy **using far-infrared ray dry sauna** was performed for patients with chronic fatigue syndrome (CFS). Symptoms such as fatigue, pain, and low-grade fever were dramatically improved on two patients. And prednisolone administration was discontinued and became socially rehabilitated 6 months after discharge.

https://pubmed.ncbi.nlm.nih.gov/17561703/

Hyperthermia for Lyme and related tick-borne illnesses

- Extreme whole-body hyperthermia up to approximately 41.6°C is directly combined with the antibiotic Ceftriaxon, ß-Lactam, and Metronidazol.

- Treatment results of 809 patients of the past 3 years showed a very good - good clinical outcome in approximately three-quarters of the patients, measured by a reduction of Burroscano-Score of at least 50%.

Dr. med. Friedrich R. Douwes

The Future of Depression Treatment?

- Whole-body hyperthermia (WBH) is promising as a safe and rapidly acting treatment for depression, with long-lasting benefits after a single session, compared with placebo. The findings are published in *JAMA Psychiatry*.
- In humans, exposure to cutaneous heating (41°C) activates the mid orbitofrontal cortex, the pregenual anterior cingulate cortex, and the ventral striatum, with the degree of activation being associated with subjective pleasantness ratings made in response to the warm temperature.

Clemens W. Janssen, PhD, from the Department of Human Development and Family Studies at the University of Wisconsin-Madison

TREATMENT OF HIV

- For treating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8+ T-cell around one month after the core temperature of the patient has been raised and returned to normal at least one time.

https://europepmc.org/article/PAT/WO0203879

Conclusion

- The current findings justify using **hyperthermia** as part of standard treatment in tumor sites for which its efficacy has been proven and, furthermore, to initiate new studies with other tumors.

- Hyperthermia is certainly a promising approach and deserves more attention than it has received until now.