En berättelse om att kombinera Hypertermi med strålterapi.

Tillägnad minnet av pionjären i klinisk hypertermi MD PhD Claes-Ebbe Lindholm 2024

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A Story of Combining Hyperthermia with Radiation Therapy

Dedicated to the memory of the pioneer of clinical hyperthermia MD, PhD Claes-Ebbe Lindholm †2024

Bertil RR Persson

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LUND 2025

In memory of

MD, PhD Claes Ebbe Lindholm

Birth: July 23, 1937

Death: December 25, 2024

During the early 1980´s, oncologist Claes-Ebbe Lindholm participated in the development of microwave-induced hyperthermia in combination with radiotherapy for the treatment of superficial breast cancer recurrences at the oncology clinics in both Malmö and Lund. The results were compiled by him in a doctoral thesis in 1992.

In 1995, Claes-Ebbe Lindholm and colleagues summarized the experiences of prognostic factors for tumor response and skin damage in combined radiotherapy and hyperthermia for superficial recurrent breast cancer (Lindholm et al., 1995).

Prognostic factors for complete tumor response and acute skin damage in combined hyperthermia and radiotherapy were analyzed from patients with recurrent breast cancer in previously irradiated areas. Radiation therapy was given daily at 2 Gy to a total absorbed radiation dose of 30 Gy after 2 weeks or 34.5 Gy after 3 weeks of treatment. The complete response (CR) in 49 of 69 evaluable patients was 71%.

He performed an outstanding pioneering work that forms the basis for a future revolutionary combination of Hyperthermia and ultra-hypo-fractionated Radiotherapy with Immunotherapy.

A true pioneer and a true joy-maker has left children with families, patients, friends and colleagues in great sorrow and loss.

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A story about combining Hyperthermia with Radiation Therapy

Bertil RR Persson

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Summary:

This story is about how hyperthermia (heating of tumors) can be used together with radiation therapy to improve treatment results in cancer, especially recurrent breast cancer. New combination methods with immunotherapy are also proposed to further enhance the effect and improve the patients' prognosis.

The story is a tribute to the memory of the pioneer oncologist Claes-Ebbe Lindholm, who was a central figure in the research and clinical application of microwave-induced hyperthermia in Skåne.

Hyperthermia has been used for the treatment of cancer as early as the 19th century, but modern methods with microwave-induced hyperthermia were developed during the 1980s in Lund and Malmö.

Microwave-induced hyperthermia was combined with radiation therapy, which improved tumor response and increased the chance of remission. Clinical studies in Lund and Malmö showed that this combination treatment had a better effect on superficial tumors than radiation therapy alone.

Despite the good clinical results, however, no oncology clinic in Sweden has continued to use the method. In the rest of Europe, however, a few oncology clinics have included hyperthermia treatment in their repertoire.

Continued research after the turn of the millennium has shown that hyperthermia affects the tumor environment, including by increasing blood flow, improving oxygenation and enhancing the effect of radiotherapy. Studies that are more recent have also shown that hyperthermia can activate the immune system, which may contribute to a better long-term prognosis.

Recently, a method with water-filtered infrared hyperthermia (wIRA) in combination with Hypo-Fractionated radiotherapy with 4 Gy once a week to a full dose of 20 Gy, has shown good results for patients with recurrent breast cancer.

Good treatment results of superficial recurrent breast cancer have been reported with combined conventional low-dose radiotherapy and microwave-induced hyperthermia. Therefore, microwave-induced hyperthermia should also be considered in combination with ultra-hypo-fractionated radiotherapy (UHFRT).

Fractional radiation doses up to 8 Gy could be divided into two separate sessions, with half the fractional dose before and half the dose after the hyperthermia treatment, with all three repeated once a week:

1 Radiation therapy (4-8 Gy)/2
2 Hyperthermia 45 - 60 min to tumor temperature: 42 - 43°C
3 Radiation therapy (4-8 Gy)/2

This would avoid the question of whether hyperthermia should be administered before or after radiation therapy. In addition, there would be great opportunities to individualize the treatment according to the tumor size and response by varying the fractional radiation dose and the number of treatments to a maximum of 24 Gy full dose.

Clinical studies in Greece of *Non-Small Cell Lung Cancer* and *Head and Neck Cancer* with antiPD1 immunotherapy in combination with 2-3 fractions of ultra-hypo-fractionated radiation therapy with only one radiation fraction of 5-8 Gy per week showed high objective response rates (>80%), good tolerability and long-term local control.

This opens up future possibilities to combine hyperthermia with ultra-hypo-fractionated radiation therapy and immunotherapy.

I. Hyperthermia treatment of tumors in Lund

One day sometime in the late 1970s, I was standing at an experimental setup to study the blood flow in a tumor in a rat using radioactive particles. Next to me was the associate professor of Surgery Lars-Olof Hafström (he was simply called LO) who had just returned from a study visit to Texas with Professor Giovanella (Sundqvist et al., 1978, Hafstrom et al., 1980b).

There he had gained insight into how to treat malignant melanoma with hyperthermia, i.e. heating to a body temperature of about 42-43• C in combination with chemotherapy.

Hyperthermia was used for tumor treatment as early as the 19th century when the patient was injected with Coley's toxin, which was supposed to contribute to tumor regression through high fever caused by the infection caused by the pyrogenic substance (Baronzio, 2006).

In 1898, Westermark presented the use of localized hyperthermia in Sweden to produce tumor regression in patients with cervical carcinoma (Westermark, 1898).

In 1935, Warren presented encouraging results from patients with advanced cancer treated with a combination of heat, induced with a pyrogenic substance, in combination with X-ray therapy. In a total of 32 patients, 29 improved within 1 to 6 months (Warren, 1935).

LO told me that in his endeavor to conduct hyperthermia experiments in Lund, he tried to increase the temperature in tumors in rats using a heat lamp. However, the rats got burned in the ears and no further increase in blood temperature was achieved. Then I suggested that he try heating the rats with microwaves, which physiotherapists use to treat stiff muscles.

We acquired a used Siemens 2450 MHz microwave equipment for Physiotherapy and tried to regulate the heating to the desired temperature with a thermocouple and a temperature relay. But it turned out to be completely impossible to get the analog electrical relay to work together with the microwaves.

I had a doctoral student, Magnus Bolmsjö, who, together with the professor of Neurophysiology David Ingvar, studied blood flow in the brain with radioactive Xenon-isotopes.

Magnus' hobby was to tinker with ingenious electronic devices, for example to regulate the ignition in car engines. I asked him if he had any ideas on how to regulate the microwave generator. He remembered that he had read something in

an American electronics magazine about an electronics kit for a digital device that could possibly be used. After some time, a package arrived with a 4-bit Z80 microcomputer that Magnus tinkered with a thermistor as a sensor for a digital temperature regulator.

Coincidentally, a course was organized at Lund University of Technology (LTH) for programming this particular microcomputer. We immediately signed up for the course, which actually aimed to engineers at various companies in Skåne. We learned how to program traffic light signals with assembler written in ASCII characters.

The engineers felt it was more like a playhouse and did not show much enthusiasm for using the microcomputer. However, Magnus became very enthusiastic and managed to program the microcomputer to regulate the microwave generator so that it worked without interference. Unfortunately, we did not have the sense to patent the device (Bolmsjo et al., 1982).

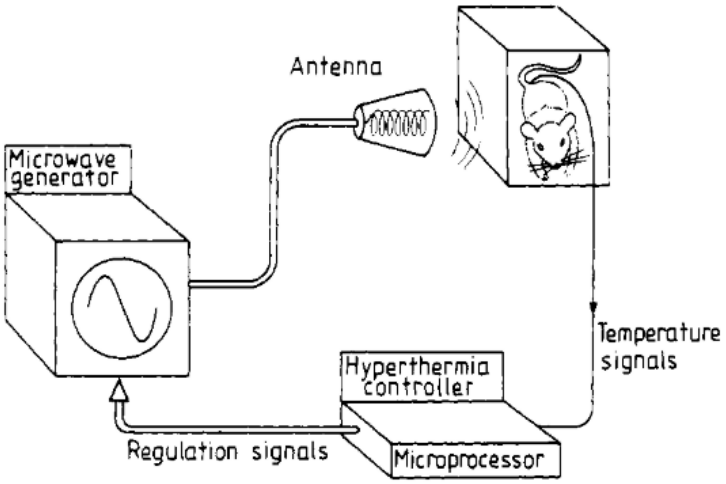
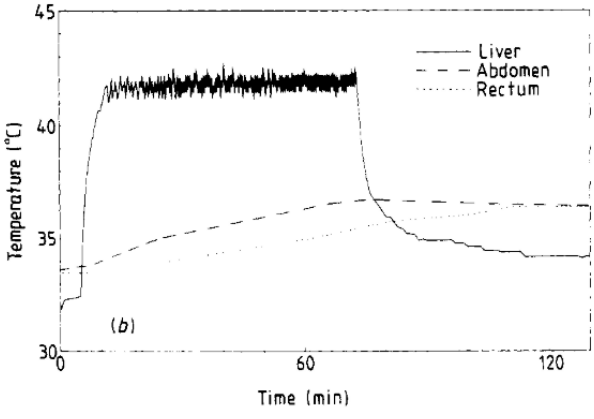


Figure 1

Block diagram of the hyperthermia system. The control unit controls the microwave power to maintain a constant temperature in the animal.
(Bolmsjo et al., 1982)

LO was now able to conduct his rat experiments with the device shown in Figure 1 with full temperature control as shown Figure 2.



Figur 2

Temperaturprofiler, systemisk hypertermi.

I abdomen och rectum hos en råtta. Temperaturen varierade mellan 41,5°C - 42°C i den hypertermi exponerade råttans lever (Bolmsjo et al., 1982).

LO developed the hyperthermia method for clinical perfusion treatment of patients with malignant melanoma (Bagge et al., 2014, Rizell et al., 2008, Lindnér et al., 1999, Hafstrom and Naredi, 1997).

Several of LO's doctoral students continued to develop the hyperthermia method for the treatment of liver tumors (Hafstrom et al., 1980a, Hafstrom et al., 1980b, Ryden et al., 1982, Bengmark et al., 1982, Hugander et al., 1983, Erichsen et al., 1985, Moller et al., 1995, Moller et al., 1996, Tranberg et al., 1996, Ivarsson et al., 2003b, Ivarsson et al., 2003a, Ivarsson et al., 2005, Jönsson and Axelsson, 2007).

II. Microwave Hyperthermia and Radiation Therapy 1980 – 1995

In my actual profession in medical radiation physics, there was a close collaboration with clinical radiation therapy. After undergoing surgery and radiation therapy for breast cancer, some patients developed recurrent tumors in the chest, so-called recurrences, which were difficult to treat because the patient had already received full-dose radiation therapy (approx. 60 Gy).

Another of my doctoral students, Per Nilsson, together with oncologist Lisa Kjellén, showed interest in testing whether a combination of microwave-induced hyperthermia and low-dose radiation therapy (30 Gy) could be used to treat breast cancer recurrence.

Tumors implanted on the flanks of mice were treated with a special microwave applicator. After it was shown that the tumors disappeared in some mice treated with a combination of hyperthermia and radiation therapy, the method was developed for the treatment of patients.

For the induction of hyperthermia in clinical practice in Lund, we developed a 2450 MHz microwave system, which began clinical use in August 1980. In

1982, the hyperthermia system was developed to use the more deep-acting frequency of 915 MHz, and in 1986, 434 MHz also became available.

The digital control system adjusts the temperature in the tissue by alternating temperature recording and microwave irradiation. Conventional thermistor probes (diameter 0.6 mm), which are placed in the tissue with intravenous cannulas, were used for temperature control.

With a waveguide applicator connected to the microwave equipment, tumors were treated locally in patients with breast cancer recurrence (Nilsson and Persson, 1985, Nilsson et al., 1982). For Research Day 1983, I was assigned to demonstrate the hyperthermia equipment to H.M. King Carl XVI Gustav and H.M. Queen Silvia.

Figure 3

Research Day in Lund 1983, at my presentation of our first hyperthermia treatment equipment with the IMSAI computer for H.M. King Carl XVI Gustav. In my left hand I hold the patient applicator.

Magnus Bolmsjö formed a company Lund Science AB that manufactured the "Hyperthermia System 4000" which was a 915 MHz system for hyperthermia treatment of superficial malignant tumors, down to a depth of 3-4 cm.

Hyperthermia system 4010 was installed and used for tumor treatment, among others, at the oncology clinics in both Malmö and Lund. There, during the 1980s and 1990s, successful treatment of breast cancer recurrence in combination with radiotherapy was carried out (Lindholm et al., 1982a, Lindholm et al., 1983, Lindholm et al., 1985, Lindholm et al., 1982b).

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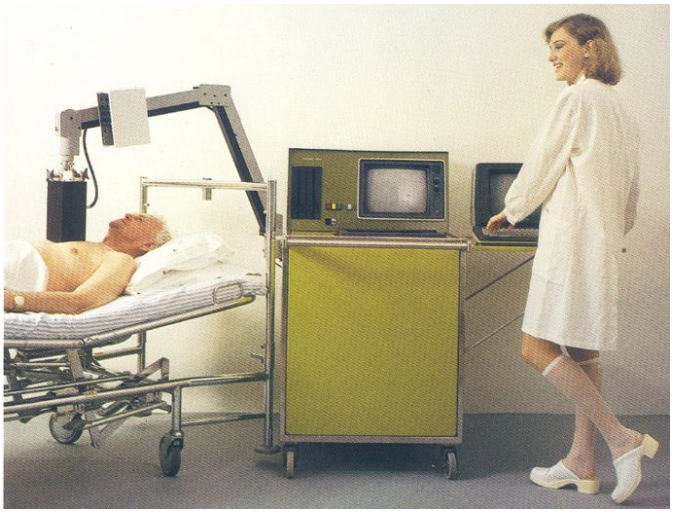

Figure 4
The first version of the *Hyperthermia system 4000* with my father Arthur Persson as a demo patient.

Figure 5
A more modern version of *Hyperthermia System 4010*.

From August 1980 to November 1984, a total of 85 superficial recurrent breast tumors, mainly adenocarcinoma (78%), were treated in Lund and Malmö. In 38 patients with either combined local hyperthermia, 41-45°C for 4 sessions and o full dose of 30 Gy radiation therapy or the same low-dose radiation therapy alone. The treatment was given for two weeks. Hyperthermia was induced externally with 2450 MHz or 915 MHz microwaves.

A total of 57 tumors received combined treatment with a complete cure rate of 46% (duration 1-38 months) and partial response rate of 30%.

In 18 patients with 2-10 superficial tumors each, 56 tumors were used in a comparative study, where the effect of combined hyperthermia and full-dose of 30 Gy radiation therapy was compared with the same low-dose radiation therapy alone, where the patients were their own controls. The overall response rate was 89% in the combined group and 50% with radiotherapy alone. The difference in response rate in favor of the combined treatment is significant ($p=0.004$), and when comparing only the complete remissions, $p = 0.0027$.

These results encouraged further development of hyperthermia therapy by using multiple applicators in phase and lower frequencies to reach deep-seated tumors, and by developing methods for non-invasive temperature monitoring.

In collaboration with the University of Amsterdam, Lund Science developed a 70 MHz microwave system that could treat deep-seated tumors (van Dijk et al., 1990).

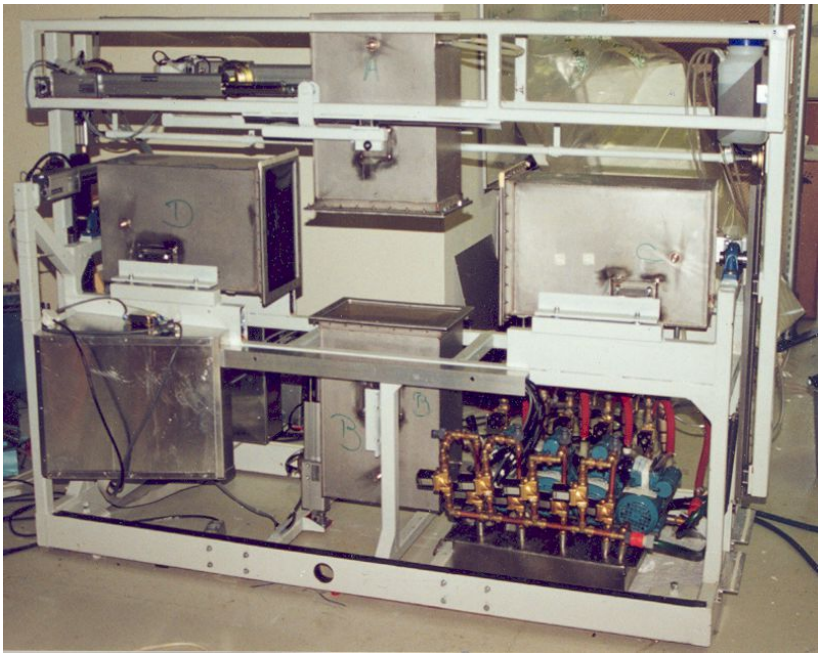

Figure 6

An early version of the Amsterdam 70 MHz microwave treatment system that could treat deep-seated tumors with 4 large applicators
(van Dijk et al., 1990).

In addition to the *Hyperthermia system 4010*, the 70 MHz system was also delivered to a Cancer Clinic in Milan and to the Pope's Hospital in San Giovanni Rotondo on the heel of Italy on the Aegean Sea.

The University of Madison, Wisconsin, USA, was in the 1980´s the site of the most progressive clinical hyperthermia research, and considered as the "*Mecca of Hyperthermia*". I went there on sabbatical leave in 1985 and became involved in a clinical hyperthermia control program travelling around the USA checking the function and standards of hyperthermia equipment at various clinical institutions, including the City of Hope clinic in California.

In Madison, the focus was on whole-body hyperthermia, where an infrared heater was modified for clinical use. It was basically a stainless steel cylinder that was heated to 60°C with electrical cables, into which the patient was inserted and warmed to 42°C body temperature in combination with chemotherapy (Robins et al., 1989).

Summary of the clinical results in Malmö and Lund

In 1995, Lindholm and colleagues summarized the experience of prognostic factors for tumor response and skin damage in combination radiotherapy and hyperthermia for superficial recurrent breast cancer (Lindholm et al., 1995).

Prognostic factors for complete tumor response and acute skin damage in combination hyperthermia and radiotherapy were analyzed in patients with recurrent breast cancer in previously irradiated areas. Radiation therapy was given daily in 2 Gy fractions to a total absorbed radiation dose of 30 Gy in 2 weeks or 34.5 Gy in 3 weeks.

- Schedule A: The first radiotherapy regimen with applied heat twice a week for two weeks.
- Schedule B: The second radiotherapy regimen was combined with hyperthermia either once or twice a week, resulting in a total of three heat treatments, or
- Schedule C: with six heat treatments.

Hyperthermia was induced with microwaves (2450, 915 or 434 MHz) via external applicators and was always given after radiotherapy. The complete response (CR) rate was 71% in 49 of 69 evaluable patients. There was no significant difference in CR rate between the three hyperthermic regimens. For each regimen, the rates of complete remission (CR) for the different treatment regimens were:

- Schedule A: 74% (14/19),
- Schedule B: 65% (15/23),
- Schedule C: 74% (20/27). (Lindholm et al., 1995).

Despite the good treatment results, the method was considered too resource-intensive for clinica routine, so hyperthermia treatment in combination with radiotherapy became not continued in Sweden.

III. Hyperthermia and radiotherapy in the 2001th century

Peeken, in 2017, discussed the use of hyperthermia in modern radiation oncology (Peeken et al., 2017).

In addition to enhancing the effect of radiation, hyperthermia causes changes in perfusion, oxygenation, and inhibition of DNA repair mechanisms. There are also indications for immune-stimulation and induction of systemic immune responses.

However, despite the increasing number of robust clinical studies, only a few oncology clinics have included hyperthermia treatment in their repertoire. Over the years, however, abundant prospective and randomized clinical data have emerged showing a clear benefit of combined hyperthermia and radiation therapy for superficial breast cancer recurrence, cervical cancer, or cancer of the head and neck region.

In conclusion, Peeken argued that in conjunction with targeted systemic therapy and improved chemotherapy for micro-metastatic disease, hyperthermia treatment for local control may have clinical significance (Peeken et al., 2017).

Notter and colleagues presented in 2020, an evaluation of therapeutic outcomes of combined infrared-induced hyperthermia (wIRA) and hypo-fractionated reirradiation in the treatment of local breast cancer recurrence (Notter et al., 2020).

High overall response rates of complete remissions were achieved even in large tumors after the application of non-contact, thermography-controlled water-filtered infrared superficial hyperthermia (wIRA), immediately followed by hypo-fractionated low-dose reirradiation, consisting of 4 Gy once a week up to a total dose of 20 Gy,

Effective tumor control in patients suffering from inoperable locally recurrent breast cancer (LRBC) in previously irradiated areas with previous total doses of 60–66 Gy can thus be successfully re-treated with low-dose irradiation in combination with superficial hyperthermia.

However, comparability of clinical data between different combined treatment regimens of hyperthermia (HT) in combination with radiotherapy (RT) is hampered by the highly individual characteristics of recurrent breast cancer (LRBC).

Tumor size, which varies from microscopically small lesions to large-scale cancer *en cuirasse*, is described as one of the most important prognostic factors. However, in clinical studies and analyses of LRBC, tumor size has been reported to date in a very heterogeneous manner. Therefore, Notter developed a simple feasible size classification for the evaluation of the 201 patients included in the study.

The size classification proves to be well feasible and allows the assessment of the benefits and limitations of the combination HT+RT in the treatment of different tumor sizes. It also improves the comparability of data and the stratification of prognosis groups, which helps to guide the decision between curative and palliative intent of the treatment.

Using this classification, the retrospective analysis of 201 patients treated with non-contact, thermography-guided wIRA-HT immediately followed by hypofractionated RT for 5 weeks with 4 Gy, once weekly, results in a high clinical overall response rate and a satisfactory local control rate even in large tumors of LRBC. Low toxicity allows repeated reirradiations in case of new relapses.

The tumor response rate of complete remissions (CR rate) decreased with increasing tumor extent:

76% in rClass I, tumor extent < 100 cm^2
61% in rClass II tumor extent >100 cm^2
36% in rClass III. II + tumor on contralateral chest wall or abdominal wall
1 CR in rClass IV. III + tumor on the back.

Similarly, the partial tumor response rate (PR rate) correlated with tumor size.

The objective tumor response rate OR(CR + PR) was100 % in rKlass I, and

97 % in rKlass II,
97 % in rKlass III,
85 % in rKlass IV. (Notter et al., 2020)

Van Dieren and colleagues presented a systematic review in 2024 of immunological synergies to enhance radiation-induced abscopal effects with combined radiotherapy and hyperthermia (Van Dieren et al., 2024).

The abscopal effect is a systemic immune response characterized by metastasis regression at sites distant from the irradiated lesion. Their systematic review aims to explore the immunological mechanisms underlying the abscopal effect and to investigate how hyperthermia (HT) can increase the chances of radiotherapy (RT) triggering systemic antitumor immune responses.

Their review indicates that HT and RT have both complementary and synergistic immunological effects. Both methods trigger the release of danger signals (DAMPs), which promote cytokine and chemokine secretion, leading to increased T-cell infiltration into the tumor and facilitating cell death.

Both treatments upregulate the extracellular Heat Shock Protein HSP70, which can enhance DAMP recognition by macrophages and dendritic cells DC, leading to stronger tumor antigen presentation and CTL-mediated immune responses.

In addition, the combined increase in cell adhesion molecules (VCAM-1, ICAM-1, E-selectin, L-selectin) can enhance leukocyte adhesion to tumors, enhance lymphocyte trafficking and increase systemic antitumor effects.

In addition, HT causes vasodilation and improves blood flow, which can enhance the Abscopal effect. They suggest the combination of local radiotherapy with extensive whole-body hyperthermia to optimally improve the chances of triggering the abscopal effect mediated by the immune system (Van Dieren et al., 2024).

Although the tumor and its microenvironment (TME) are highly immunosuppressive. due to the secretion of TGF-ß and the presence of MDSC, M2-type macrophages and T_{regs}, the combined approach indicates a reduction in immunosuppression.

Therefore, the ability to make the immunosuppressive TME more immunostimulatory should be further explored. Studies are warranted to confirm that the immunological potential of combined HT + RT, offers hope for innovative cancer treatments (Van Dieren et al., 2024).

IV Clinical trials with combined Immuno-Radiation Therapy

Persson presented a story in 2025 about combining immunotherapy with ultra-hypofractionated radiotherapy in the journal “Acta Scientiarum Lundensia” (Persson, 2025).

In preclinical animal models, combined radiotherapy and CTLA-4 blockade can induce tumor regression and reduce metastases (e.g. lung metastases).

Hypofractionated radiotherapy (e.g. 8 Gy×3 fractions) is particularly effective in inducing abscopal effects, which involve immune responses even outside the radiation field (Formenti, 2017). Mechanisms such as the cGAS-STING pathway and the enzyme Trex1 influence the immune response to radiation.

PD1 blockade in combination with Ultra-Hypo-fractionated radiation (8 Gy × 3) increases antitumor immunity and abscopal effects. The combination activates killer T-cells and reduces immunosuppressive myeloid-derived suppressor cells (MDSC). Dendritic cell vaccines can improve the immune response, but their clinical efficacy is still limited.

However, clinical trials of PD1 blockade in combination with conventional radiotherapy have not shown significant improvements in progression-free survival (Lee et al., 2021). The effect of radiation on tumor-draining lymph nodes is also thought to negatively affect the efficacy of immunotherapy (Koukourakis and Giatromanolaki, 2022).

Hypo-Fractionated radiotherapy, where fewer but higher fraction doses of radiation are used, was compared with conventional fractionation for various cancers.

However, clinical trials of Ultra-hypo-fractionated radiotherapy, with only one 8 Gy fraction per week, can potentially enhance the effect of immunotherapy by reducing the tumor's immunosuppressive environment and stimulating anti-tumor immunity.

Combination treatment of head and neck cancer with Nivolumab and 2-3 fractions of ultra-hypo-fractionated radiotherapy showed high objective response rates (80%) and good tolerability (Koukourakis et al., 2023).

Combination treatment of Non-Small Cell Lung Cancer with Ultra-hypo-fractionated radiotherapy combined with anti-PD1 immunotherapy yielded an objective response rate of 81.8% and long-term local control (Filippatos et al., 2023).

V. Epilogue

Notter and colleagues presented in 2020 an evaluation of therapeutic results of non-contact, thermography-controlled water-filtered infrared-superficial hyperthermia (45 - 60 min to tumor temperature: 42 - 43°C), immediately followed by hypo-fractionated reirradiation, consisting of a 4 Gy fraction of radiation. This was repeated four times once a week up to a total dose of 20 Gy, resulting in high overall response rates even in large tumors (Notter et al., 2020).

Good treatment results of superficially recurrent breast cancer have also been reported with combined conventional low-dose radiation therapy and microwave-induced hyperthermia (Lindholm et al., 1995). Therefore, microwave-induced hyperthermia should also be considered in combination with ultra-hypo-fractionated radiation therapy (UHFRT).

With increased fractional radiation dose up to 8 Gy, the treatment could be divided into two stages with half the fractional dose before and half the dose after, and the hyperthermia treatment in between with att three given once a week:

1 Radiation therapy (4-8 Gy)/2
2 Hyperthermia 45 - 60 min to tumor temperature: 42 - 43°C
3 Radiation therapy (4-8 Gy)/2

This would avoid the question of whether hyperthermia should be administered before or after radiotherapy. In addition, there would be great opportunities to individualize the treatment according to the size and response of the tumor by varying the fractional radiation dose and the number of treatments to a maximum full dose of 24 Gy. Studies are warranted to confirm whether the immunological potential of combined microwave-induced HT+UHFRT can be used routinely in cancer treatments.

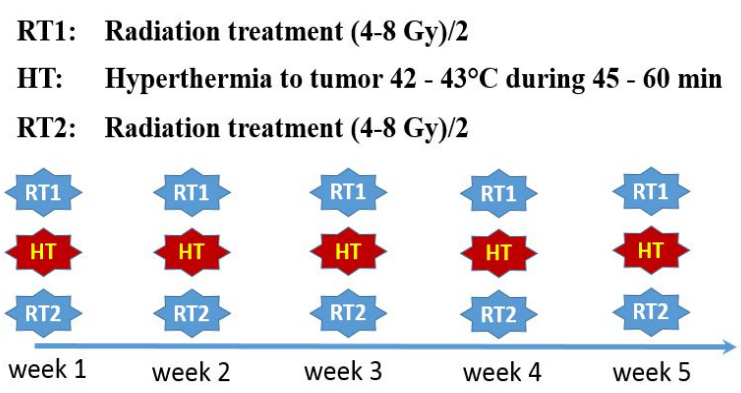

Figure 7
Microwave-induced hyperthermia in combination with ultra-hypo-fractionated radiotherapy with division of fractional radiation dose (4-8 Gy per fraction) in two stages with half the fractional dose before and half the dose after the hyperthermia treatment once per week up to a total radiation dose of maximum 24 Gy.

For patients with limited options with relapse after previous treatments, retreatment with Ultra-Hypo-fractionated radiotherapy shows promising results in combination with anti-PD1 immunotherapy (Koukourakis et al., 2023). The increased tolerability and improved immune response support further studies of microwave-induced hyperthermia treatment protocols (Persson, 2025).

A combination of regional microwave-induced hyperthermia and Ultra-hypo-fractionated radiotherapy, consisting of 4-8 Gy once a week in combination with anti-PD1 immunotherapy should result in even better response rates even with limited anti-PD1 treatment to reduce immune-related adverse events (irAE).

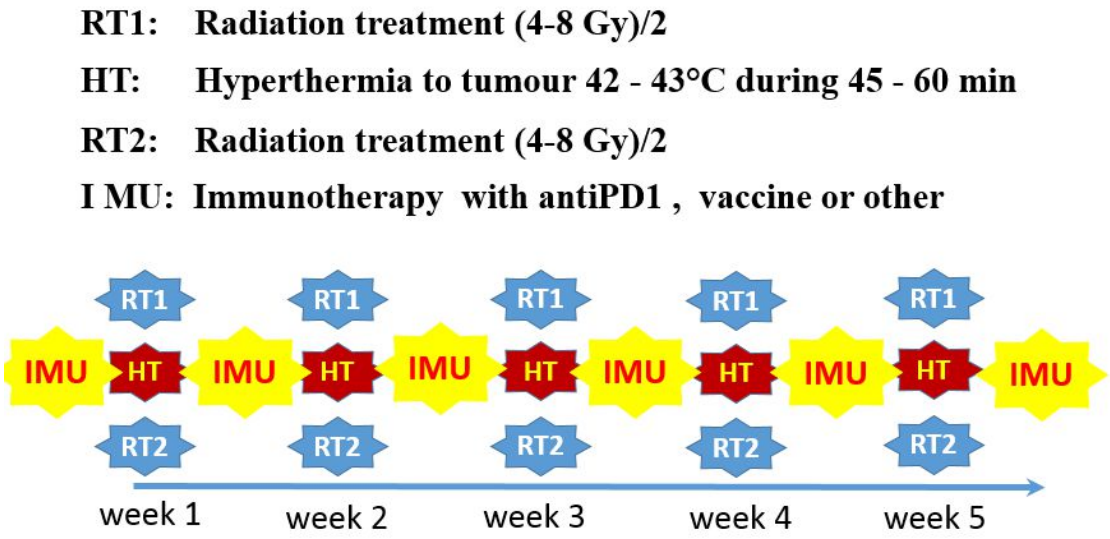

Figure 8

Microwave-induced hyperthermia in combination with ultra-hypo-fractionated radiotherapy with division of fractional radiation dose (4-8 Gy per fraction) in two stages with half the fractional dose before and half the dose after the hyperthermia treatment once a week in combination with e.g. anti-PD1 immunotherapy (IMU) to a full dose of max. 24 Gy.

Although anti-PD1 immunotherapy is well tolerated, it has a unique side effect profile with immune-related adverse events (irAEs). Adverse effects of immunotherapy are most commonly observed in the skin, gastrointestinal tract, liver, lungs and endocrine systems. Less common side effects may include neurological, hematological, cardiac, ocular or rheumatological involvement (Barquín-García et al., 2019).

Other clinically validated Immunotherapy regimens (IMU) may therefore also be considered such as Tumor and Dendritic Vaccine or others (Persson, 2025).

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