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Table of content

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Summary

A story of a Royal Meeting that created Intermittent Radio Therapy

Prologue

Microwave hyperthermia and radiation therapy (1980–1990)

My early research in medical radiation physics led to develop the combined treatment of breast cancer recurrence with microwave-induced hyperthermia and low-dose radiation (30 Gy). Clinical trials were initiated with patients who had previously received a full radiation dose (60 Gy). The hyperthermia equipment we developed was presented to King Carl XVI Gustaf and Queen Silvia at the Research Day in Lund in 1983. At the same time, Leif G. Salford presented an idea for treating brain tumours with magnetic particles loaded with cytostatic agents – this meeting led to a long-term and fruitful research collaboration between Persson and Salford.

The BRIGTT-study ("Brain Immune Gene Tumour Therapy")

The aim of that study was to investigate the ability of T cells (CTL) to fight glioma via vaccination with the patient's own tumour cells. The cells were modified to secrete interferon-gamma and then irradiated to prevent growth in the patient. The vaccine was injected into the skin of the arm, which activated the immune system against brain tumours. A clinical study with 8 vaccinated patients resulted in significantly longer median survival (488 days) for vaccinated patients compared to an unvaccinated control group (271 days).

Combination of immunotherapy and radiation therapy

Intracranial tumour model (N29 and N32 glioma)

Glioma tumour (N29) inoculated into the brain of rats was treated with a vaccine of syngeneic tumour cells gene-transfected with INFγ, in combination with a single radiation fraction of 5 or 15 Gy. The rats were divided into different groups according to:

- No treatment
- Radiation therapy (5 or 15 Gy)
- Immunization with IFN-gamma-secreting syngeneic tumour cells
- Combination of radiation therapy and immunisation
- Best survival (75%) was achieved with a single radiation fraction of 5 Gy in combination with immunisation.

Contemporary studies and international findings

Graf et al. (2002): et al. (2002): Immunization could increase tumour progression but in combination with radiation remission was achieved in ~50% of the rats

Lumniczky et al. (2002): Combination of cytokine-expressing cancer vaccines (e.g., GM-CSF, IL-4) and radiation eliminated up to 100% of tumours in mice.

These findings demonstrate the potential of immunotherapy as an adjuvant to a single fraction of 5 Gy radiation in glioma treatment.

International presentation and later development

The results of the Lund study were presented first in 2003 at a conference in the USA and also in 2008 in China. With support from American researchers, the results became published 2010 in the scientific journal Radiation Research.

After 20 years, Intermittent radiotherapy in combination with hyperthermia or immunotherapy has been successfully clinically tested in Switzerland and Greece (although not in glioma patients).

Clinical Intermittent Radiation Therapy

Intermittent radiotherapy combined with hyperthermia

Van Dieren presented the following results in 2024:

Combination of radiotherapy (RT) and hyperthermia (HT) enhances immunological abscopal effect, increases T-cell infiltration, DAMP signalling and CTL responses. Furthermore, immuno-Suppression in the tumour microenvironment (TME) is reduced. In addition, blood circulation is improved through vasodilation.

Notter and colleagues in Bern presented the following results in 2020:

Intermittent-Radiation fractions of 4 Gy/week combined with non-contact hyperthermia for five weeks resulted in a high rate of complete response even in large previously irradiated breast tumours.

Intermittent radiation combined with Immunotherapy (Anti-PD-1)

Koukourakis and colleagues in Athens presented the following results in 2023:

Intermittent radiotherapy (8 Gy/week) combined with Nivolumab immunotherapy resulted in a 41.2% complete response (CR) in previously irradiated Head and Neck tumours, with good tolerance, low toxicity, and 3-year survival rates of 50% and progression-free survival rates of 35%.

Filippatos and colleagues in Athens presented the following results in 2023:

Intermittent-Radiotherapy with 1–2 fractions of 8 Gy/week combined with anti-PD-1 Immuno-therapy resulted in 27.2% complete response (CR) in previously irradiated non-small cell lung cancer. Some patients showed immune-related side effects (36% discontinued immunotherapy). The two-year survival was 62%.

Radiation therapy only

Astrid Persson and colleagues presented 2024 the 10 years results of a phase III study

Results of 600 men with prostate cancer who received Ultra-Hypo-Fractional Radiotherapy (UHF-RT) with 6.1 Gy per fraction in 7 fractions over 2.5 weeks, compared with 600 men who received conventional radiotherapy (CF-RT) with 2 Gy per fraction in 39 fractions over 8 weeks. After 10 years, the symptom-free survival was 72% in the (UHF-RT) group and 65% in the (CF-RT) group. Side effects were similar between the groups.

Results of 600 men with prostate cancer who received Ultra-Hypo-Fractional Radiotherapy (UHF-RT) with 6.1Gy per fraction in 7 fractions over 2.5 weeks), compared with the 600 men who received conventional radiotherapy (CF-RT) with 2 Gy per fraction in 39 fractions over 8 weeks.

After 10 years, the symptom-free survival was 72% in the (UHF-RT) group and 65% in the (CF-RT) group. Side effects were similar between the groups.

Epilogue

Definition of Intermittent-Radio-Therapy (iRT):

Single fractions of radiation (4–10 Gy) repeated every 2–7 days

Mechanism:

Radiation releases tumour antigens from tumour cells.
Radiation reduces the number of tumour´s immunosuppressive MDSC cells, which strengthens effect of CD8+T cells.

The time intervals between radiation fractions

allow time for toxic immune cells (CTL) to develop and attack the tumour.

Combination treatment is possible between radiation fractions:

Immunotherapy (e.g. Vaccine, Anti-PD-1) iRIT
Hyperthermia iRHT
Other immuno-stimulating treatments are also possible

Summary of all clinical treatment results

Indication	No, Fractiones	Dose	Combination	CR %
Breast cancer <100 cm² iRHT	5	4	wIRA	76
Breast cancer >100 cm² iRHT	5	4	wIRA	50
Head-Neck Ca. recidive iRIT	3	8	PD-1	50
NSCLC iRIT	2	8	PD-1	27
Prostate Ca. UHF-RT	7	6	–	72
Prostate Ca. CF-RT	39	2	–	62
Breast cancer CF-RT + microwave HT	15	2	mwHT	71

Conclusions

- Intermittent Radiation Therapy (iRT) + Hyperthermia (iRHT) shows better effect than iRT + Immunotherapy (IRIT) in some cases.
- Hyperthermia HT is an effective and cost-effective treatment method in combination with Intermittent Radiotherapy iRT.
- iRT reduces the number of treatment sessions and increases the clinic's radiotherapy capacity.
- There is a possibility to use transurethral microwave heating for prostate hyperthermia.

Chapter I
A Royal Meeting

1.1 Microwave Hyperthermia and Radiation Therapy 1980 – 1990

In my actual profession in medical radiation physics, there was close collaboration with oncology and radiotherapy.

One of my radiation physics doctoral students, Per Nilsson, along with oncologist Lisa Kjellén, expressed interest in testing whether a combination of microwave-induced hyperthermia and low-dose radiotherapy (30 Gy) could be used to treat breast cancer recurrence (Persson, 2025).

A special microwave applicator was used to treat tumours implanted on the flanks of mice. After it was demonstrated that tumours disappeared in some mice treated with a combination of hyperthermia and radiotherapy, the method was developed for treating patients. A waveguide applicator connected to a microwave equipment was developed to treat tumours locally in patients with breast cancer recurrence (Nilsson and Persson, 1985; Nilsson et al., 1982).

In collaboration with associate professor Torsten Landberg and MD Claes-Ebbe Lindholm, they started a clinical study of hyperthermia treatment of patients with recurrent tumours on the chest, so-called recurrences. These tumours were difficult to treat because the patient had already received radiotherapy with a total absorbed dose of approximately. 60 Gy (Lindholm et al., 1982).

For the Research Day 1983, I was assigned to demonstrate the hyperthermia equipment to H.M. King Carl XVI Gustav and H.M. Queen Silvia.

Figure 1-1 shows me at the Research Day 1983 in Lund, standing at the Hyperthermia presentation to H.M. King Carl XVI Gustav. On the right in the picture is the control panel for our hyperthermia equipment with the IMSAI computer, and my left hand holding the applicator for treating patients. In the background, media representatives are seen documenting the performance.

Figure 1-1

Here I am standing at the Lund University Research Day in 1983, at my presentation. The Swedish King H.M. Carl XVI Gustav is listening. Interesting.

On the right in the picture is the control panel for our hyperthermia equipment with the IMSAI computer. In my left hand I hold the applicator for treating patients.

The presentation on Research Day 1983 was also attended by the neurosurgeon Leif G. Salford, who shared his idea with both HM the King and the Queen regarding the treatment of brain tumours (Glioma) using magnetic particles infused with cytostatic drugs.

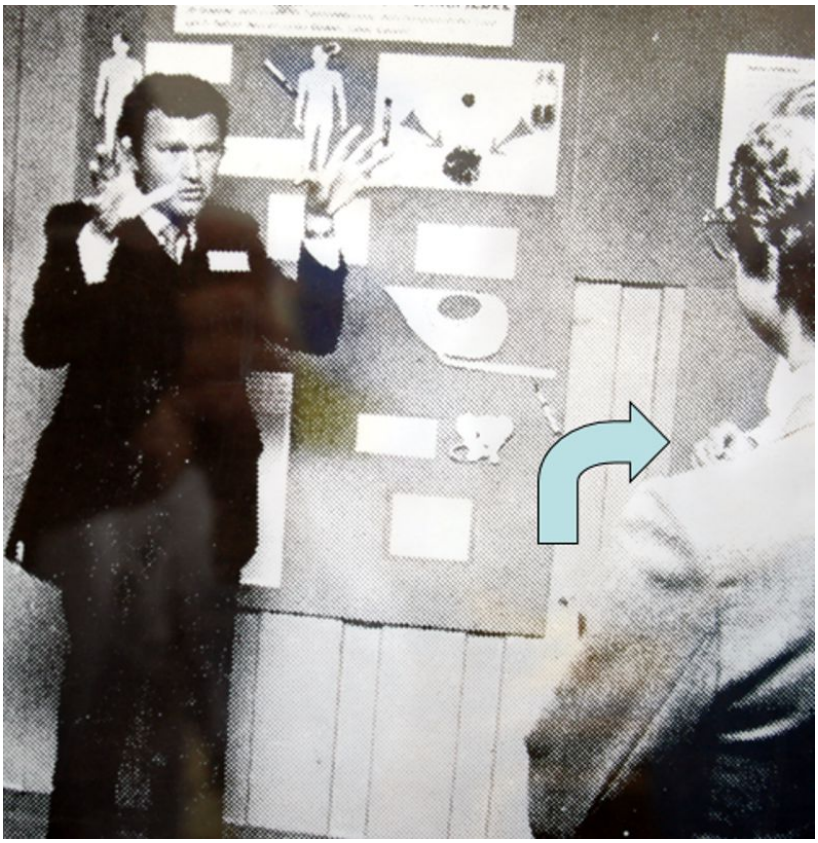

Figure 1-4

Next to me at the presentation on Research Day 1983 was the neurosurgeon Leif G. Salford, who to H.M. King Carl XVI Gustav (at the blue pointer), presenting his idea of treating brain tumours (glioma) with magnetic particles-

He had the chance to present his work once more upon the arrival of H.M. Queen Silvia.

It turned out during our conversation while waiting for the king to arrive that Leif and I had many common interests, and this royal meeting was the beginning of a long and fruitful research collaboration.

1.2 "Brain *Immune Gene Tumour Therapy*" (BRIGTT).

The immune response to the brain tumour malignant glioma (GBM) consists primarily of the tumour-killing function of activated cytotoxic T cells (CTL). Thus, a vaccination regimen that enhances the effector functions of CTL and simultaneously increases the number of lymphoid cells in the glioma would be able to provide effective therapy.

At the turn of the millennium, Professor of Neurosurgery Leif G, Salford at Lund University initiated a clinical trial that he called: "Brain Immune Gene Tumour Therapy" (BRIGTT) (Salford et al., 2001a, Salford et al., 2002, Salford et al., 2001b, Salford et al., 2022).

A specific tumour vaccine was produced based on tumour cells extracted of tumour tissue from the glioma patients he had previously operated on. After separation of the tumour cells, they were transfected with an adenovirus that had genetic information for the production of human Interferon-gamma (IFNγ). With the participation of Radiation physicists, the transfected cells were irradiated with gamma radiation to prevent the tumour cells from multiplying after administration to patients (Baureus-Koch et al., 2004). After irradiation, the cells were examined for the degree of IFNγ production, using ELISA measurements.

To patients who had experienced brain-tumour recurrence, the vaccine was administered into the skin of the arm to activate the immune system and produce specifically activated tumour-killing T lymphocytes (CTLs). These pass through the blood-brain barrier into the brain parenchyma, where they are intended to eliminate both tumour recurrence and migrating "guerrilla" cells in the surrounding brain (Salford et al., 2001a, Salford et al., 2002, Salford et al., 2001b, Salford et al., 2022).

The clinical study involved the vaccination of eight patients, aged 50 to 69 years, who had previously undergone treatment with surgery and radiotherapy according to the program without experiencing any side effects or toxicity. They were immunised between 8 and 14 times with their specific tumour vaccine. Neurological status and quality of life were unchanged during immunotherapy. The study also included a control group of nine unvaccinated glioma patients who also been previously treated with surgery and radiotherapy according to the standard program.

For the patients who were immunized with their own vaccine, the overall median survival time of the group was 488 days (16.1 months), which was significantly longer ($p < 0.05$) compared to 271 days (9.0 months) in the patients in the matched control group. The survival time of the immunized patients was also significantly longer compared to all GBM patients treated at the same clinic during the same period and to other control groups within the same age cohort (Salford et al., 2022).

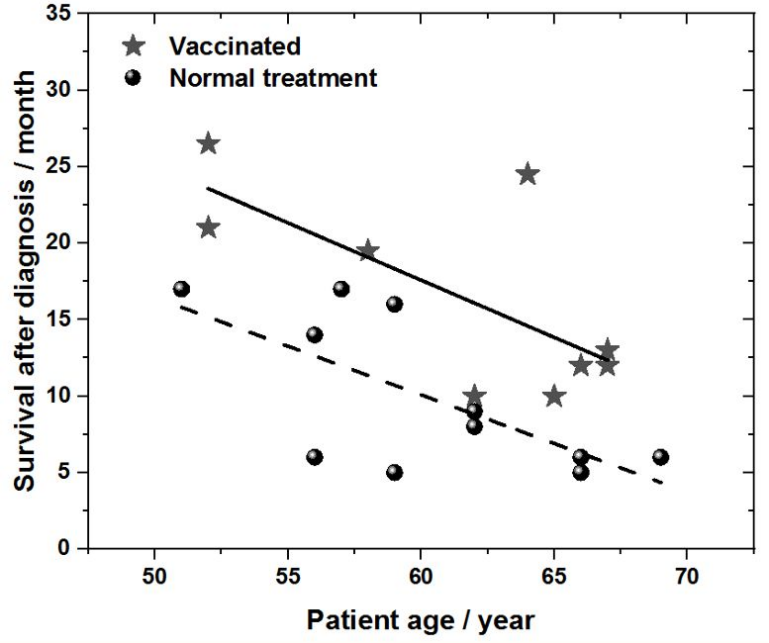

Figure 4.
Survival time after diagnosis in nine glioma patients treated with surgery and subsequent radiotherapy and with vaccination and 11 unvaccinated patients previously treated with surgery and subsequent radiotherapy (Salford et al., 2022).

Regression equations for patients of age between 50 and 70 year(a). :

★ Survival-time vaccinated = 62(±18) – 0.75(±0.29) ×Age(a) ; (month)

● Survival-time unvaccinated = 46(±12) – 0.64(±0.23) ×Age(a); (month) (dashed line) (Salford et al., 2022)

However, **Roszman** and colleagues showed in 1991 that elimination of all glioma tumour cells does not occur even when CNS tumours are exposed to large populations of T lymphocytes (Roszman et al., 1991).

This raised the question of whether immunisation with tumour vaccines could be combined with some other therapy. The closest to hand was radiotherapy, which we had previously successfully used for the treatment of breast cancer recurrence in combination with hyperthermia (Lindholm et al., 1982).

1.2 Immunotherapy with tumour vaccine in combination with radiation

Immunotherapy with interferon-gamma-secreting syngeneic tumour cells combined with radiotherapy was studied in Lund. Animal experiments with Fischer-344 rats began in 2001 with the tumour model used in the preclinical research that formed the basis of the Salford clinical BRIGTT study reported above (Persson et al., 2003).

Intracerebral tumours were inoculated into the brain of the rats with 5000 N29 tumour cells. The 46 rats involved in the study were divided into six groups, as shown in Table 1-1.

Table 1-1

The Fischer-344 rats with intracerebral N29 tumours arranged in the following groups:

Group Number	Treatment	No. Rats per Group
B1	Controls without treatment	6
B2	Radiation one fraction 5 Gy	8
B3	Radiation one fraction 15 Gy	8
B4	Immunising with vaccine 3 times	6
B5	Radiation 5 Gy + Immunisation	8
B6	Radiation 15 Gy + Immunisation	8

One week after inoculation, when the animals developed intracerebral tumours, they were irradiated, as shown in Figure 1-2, with a single fraction. The absorbed radiation dose was either 5 or 15 Gy as measured by a TLD chip placed next to the tumour during field bolus.

Within one hour after radiation treatment, half of the animals were immunised by i.p. injection of three million radiation-sterilised (70 Gy) syngeneic IFNγ-secreting N29 cells. Vaccination of the animals in was repeated 3 times: one hour after irradiation and after 14 and 28 days.

The animals were observed daily for symptoms of the growing tumours and were sacrificed when they were severely affected. The tumour was resected and examined histo-pathologically for infiltrating lymphocytes.

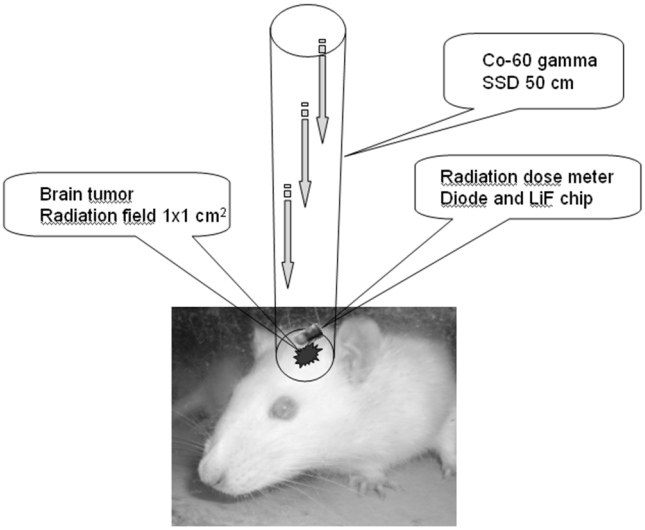

Figure 1-2
Irradiation of Intracerebral rat tumour with a radiation field size collimated to cover the entire brain (1 cm^2).
The adsorbed dose of either 5 or 15 Gy was measured using an ionization chamber and TLD dose sensor.
A 5 mm thick sheet of tissue equivalent bolus was placed over the head for radiation build-up.

Figures 1-3 show graphs of the survival time after inoculation of rats in the different groups with Controls and with the different treatments.

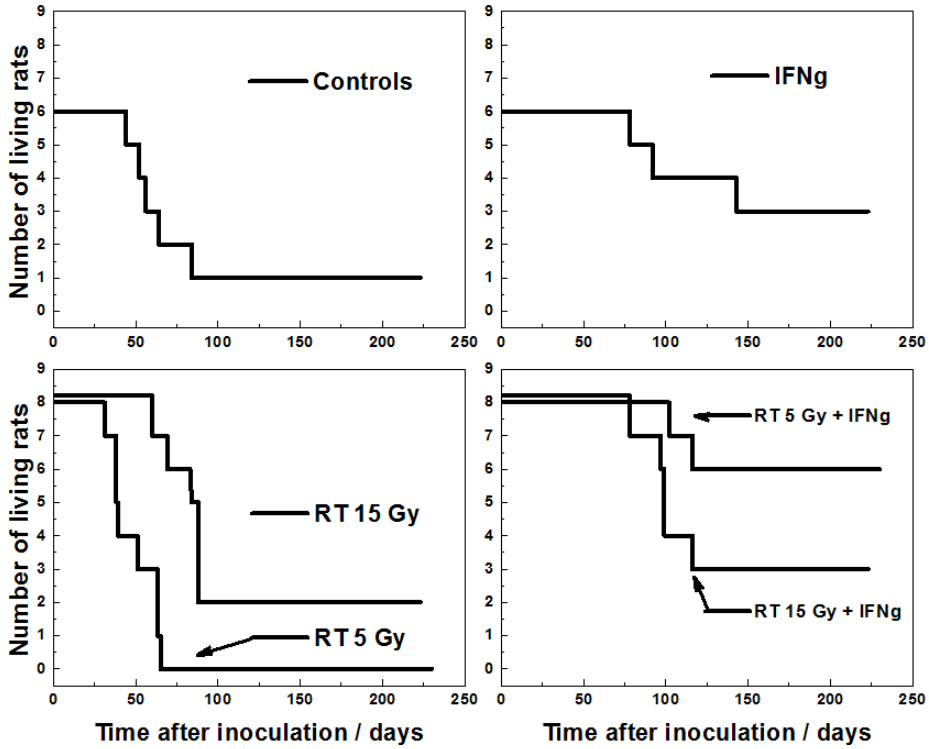

Figure 1-3
Survival plots of the number of rats with intracerebral implanted N29 tumour: controls (top left), immunisation with syngeneic N29 tumour cells (top right), radiation therapy (bottom left) and a combination of radiation therapy and immunisation (bottom right) (Persson et al., 2010).

- Of the untreated controls, one of 8 survived, which was extremely rare.
- Immunotherapy without radiation: 2 of 6 treated animals survived (about 25%).

- Radiation therapy alone once with 5 Gy resulted in no survivors,
- Radiation therapy with 15 Gy resulted in 2 of 8 animals surviving (about 25%).
- Immunisation therapy 3 times combined with 15 Gy radiation therapy resulted in 3 of 8 surviving (about 38%)
- Immunisation therapy 3 times combined with a single radiation fraction of 5 Gy in 8 treated animals resulted in 6 survivors (about 75%).

Immunization therapy combined with only one fraction of radiation with 5 Gy gave a surprisingly good result of about 75% complete remissions, which no other previous treatment of malignant gliomas had achieved.

These results were first presented at the 2003 Society of Neuro Oncology annual meeting in Keystone, USA (Persson et al., 2003).

Abstract of the conference proceedings:

In 2003, Persson, B.R.R., and colleagues Catrin Bauréus-Koch, Gustav Grafström, Per Engström, Arne Brun, Bengt Widegren, and Leif G. Salford presented the therapeutic effect of radiotherapy in combination with immunisation using syngeneic IFN-gamma-secreting tumour cells on N29 and N32 brain tumours, which were implanted subcutaneously on the flank or in the brain of Fischer 344 rats (Persson et al., 2003).

The aim was to study the therapeutic effect of radiotherapy in combination with intraperitoneal injections of syngeneic interferon-gamma-secreting tumour cells to enhance immune responses against N29 or N32 glioma tumours implanted either Subcutaneously or Intracerebrally in the brain (Caudate Nucleus) of Fischer 344 rats.

Subcutaneous glioma N29 tumours were induced by subcutaneous administration of 200,000 cells in the right leg and 50,000 cells in the left leg of syngeneic Fischer rats. After three weeks, the right tumours were treated with 4×5 Gy = 20 Gy of 60Co-gamma radiation. Immunisation was performed with in vitro-cultured tumour cells (N29), sterilised by irradiation (70 Gy), and injected intraperitoneally three times at 14-day intervals. The rats received the first immunisation five days before radiation treatment.

Immunisation with IFN-gamma-secreting syngeneic cells alone showed no significant effect on tumour growth.

Radiation treatment with 20 Gy on the right tumour resulted in a 40% reduction in growth rate on the treated side and a significant ($p < 0.001$) 30% reduction on the untreated left side.

Radiation therapy of the right tumour combined with immunisation with IFN-gamma-secreting syngeneic cells resulted in a significant ($p < 0.001$) 27% reduction in tumour growth rate for tumours on both sides.

Intracerebral tumours (N29 or N32) were inoculated into the brains of Fischer-344 syngeneic rats. After one week, the entire brain was treated with either 5 or 15 Gy of ^{60}Co gamma radiation. Once a week for three weeks, the animals received repeated intraperitoneal injections of irradiated N29 or N32 cells, respectively. The cells were genetically modified to produce interferon-gamma (IFN-gamma).

Immunisation with IFN-gamma-secreting syngeneic cells alone resulted in a significant increase in survival.

Radiation therapy alone had no clear effect on the survival of rats with N29 tumours, while a significant ($p < 0.001$) increase in survival time by 20% was recorded for rats with N32 tumours. Radiation therapy with 5 Gy for N29 and 15 Gy for N32 in combination with immunisation with IFN-gamma-secreting syngeneic cells significantly ($p < 0.001$) increased the survival of both N29 and N32 tumours. For the slowly growing N29 tumours, complete remission was observed in 6 of 8 rats (75%) treated with the combination of radiation therapy at 5 Gy and immunization.

Exposure to N29 tumour cell injection into the flank of the surviving animals 400 days after the first implantation of N29 tumour cells resulted in tumour growth in 50% of the animals (Persson et al., 2003).

The number of animals in the study was deemed too small to be suitable for a doctoral thesis. No grants were awarded to verify the effect of Intermittent Radiation Treatment or to conduct further studies with repeated fractions. As a result, the findings were left in the drawer (Luke 4:24; John 4:44).

Simultaneously, other researchers noted similar observations, and shortly thereafter, I became an emeritus professor:

Graf and colleagues presented in 2002 the results of immunisation by s.c. Injection of irradiated syngeneic tumour cells that induce localisation of T cells (CTLs) into Fischer-344 rats with intracranially implanted T9 glioblastoma tumours. However, this procedure did not lead to any curative effect and instead seemed to enhance tumour progression (Graf et al., 2002).

However, they found that the combination of immunisation with radiation exposure in rat models showed an increased therapeutic response to T9 glioblastoma, and that complete remission of tumours occurred in almost 50% of the animals. (Graf et al., 2002). In addition, the animals developed glioma-specific immunity by radiation therapy combined with cellular vaccination.

Thus, the simultaneous administration of cellular immunisation and radiation therapy inhibited the tumour from producing immunosuppressive factors, which favoured an antitumour response (Graf et al., 2002).

Lumniczky and colleagues reported in 2002 that the therapeutic effect in a mouse glioma brain tumour model (Gl261) is enhanced by combining cytokine-producing cancer cell vaccines and local conventional radiation therapy (Lumniczky et al., 2002).

They treated brain tumour-bearing mice with various cytokine-producing vaccines, prepared by in vitro transfection of GL261 mouse glioma cells with the corresponding adenoviral vectors (IL-4, IL-6, IL-7, GM-CSF, TNF• , LIF, LT). The vaccines that produced IL-4 or GM-CSF were shown to eliminate 20-40% of the tumours in the mice.

However, by combining local tumour irradiation and vaccination with syngeneic tumour cells transfected with GM-CSF, IL-4, or IL-12 vectors, approximately 80-100% of the tumours in the glioma-bearing mice were eliminated. High efficacy of the combined treatment was maintained even under suboptimal conditions where neither modality alone cured any of the mice (Lumniczky et al., 2002).

These experimental findings in rat and mouse models suggest that vaccination therapy may open up new potential in the clinical treatment of high-grade glioma when applied as an adjuvant to existing treatment modalities such as radiotherapy (Graf et al., 2002, Lumniczky et al., 2002).

However, a few years after my retirement, in 2008, my former student, Crister Ceberg, encouraged me to review the results of my studies on *Intermittent radiotherapy* after he heard from Silvia Formenti at the ESTRO meeting in Gothenburg that researchers in the USA had made similar observations in their studies of breast tumours.

Without any intervening time, I presented the results of the Lunda study at “The International Conference on Biomedical Engineering and Informatics” (BMEI 2008) in Sanya, Hainan, China (Persson et al., 2008).

The study was also published in the journal “*Radiation Research*” with the kind assistance of Silvia C. Formenti and Sandra Demaria in the USA. They observed the

same phenomenon of increased survival, studying immune-mediated inhibition of metastases following tumour treatment with low-dose local radiotherapy combined with CTLA-4 blockade or vaccination (Demaria et al., 2005; Newcomb et al., 2006; Persson et al., 2010).

Now, after 20 years, Intermittent Radiotherapy (iRT) with one fraction per week in combination with both hyperthermia (iRHT) and immunotherapy (iRIT) has been successfully clinically tested in patients with recurrent tumours (but not glioma) after undergoing conventional therapy (Notter et al., 2020, Koukourakis et al., 2023, Filippatos et al., 2023). This will be reviewed in more detail in the next chapter.

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Chapter II
Clinical Results of Intermittent Radiotherapy

2.1 Intermittent Radiation Therapy and Hyperthermia

Lindholm and colleagues summarised in 1995 the experiences from the studies in Malmö and Lund of prognostic factors for tumour response and skin damage in combination treatment with radiotherapy and hyperthermia for superficial recurrent breast cancer (Lindholm et al., 1995).

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

- Schedule A: The first radiotherapy regimen with applied heat twice per week for two weeks.
- Schedule B: The second radiotherapy regimen was combined with hyperthermia either once or twice per 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 rate (CR) was 71% in 49 of 69 evaluable patients. There was no significant difference in CR rate between the three hyperthermia treatment regimes. For each treatment, the complete remission (CR) rate for the different treatment regimens was (Lindholm et al., 1995):

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

Despite the promising treatment results, the method was considered too resource-intensive for routine clinical use, so using hyperthermia treatment in combination with radiotherapy was not continued in Sweden.

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

The abscopal effect is a systemic immune response characterised 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) may increase the capability of radiotherapy (RT) to trigger systemic antitumour immune responses.

Their review indicates that HT and RT have both complementary and synergistic immunological effects. Both methods trigger the release of danger-associated molecular patterns (DAMPs), which promote the secretion of cytokines and chemokines, leading to increased $CD8^{+}$T-cell infiltration (CTLs) into the tumour and facilitating cell death.

Both treatments upregulate the extracellular heat shock protein HSP70, which can enhance DAMP recognition by macrophages and dendritic cells (DCs), leading to stronger tumour 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 tumours, promote lymphocyte trafficking, and augment CTL´s systemic antitumour effects.

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

Although the tumour and its microenvironment (TME) are highly immuno-suppressive due to the secretion of TGF-ß and the presence of MDSC, M2-type macrophages and Tregs, the combined approach indicates a reduction in tumour immunosuppression (Van Dieren et al., 2024).

Therefore, the potential to transform the immuno-suppressive environment of tumours, the TME, into a more immuno-stimulatory state warrants further investigation. Studies are needed to confirm that the immunological potential of combined radiotherapy and hyperthermia facilitates innovative new cancer treatments (Van Dieren et al., 2024).

Sinha, and colleagues (including Jens Overgaard) presented in 2024 an in-depth critical review and the rationale for combining Hypo-fractionated radiotherapy with Hyperthermia (Sinha et al., 2024).

Conventional radiotherapy of cancer patients typically involves about 30-40 daily treatments with a radiation dose of 2 Gy five days a week. However, improved technology has now led to the increased use of fewer radiation fractions at a higher absorbed dose per fraction. This latter method is often referred to as Hypo-fractionated irradiation.

While conventional radiation therapy typically kills tumour cells by producing DNA damage, treatments involving higher doses per fraction have also been suggested to induce vascular damage. Such vascular effects will further increase the level of unfavourable micro-environmental conditions, such as hypoxia and acidity, that are already present in tumours. Cells that exist under these negative microenvironmental conditions are resistant to ionising radiation but are, in fact, sensitive to hyperthermia treatment (heating at 40-45 degrees C). This suggests that combining hypo-fractionated radiation with heat may be a viable treatment modality. Although preliminary preclinical and clinical studies are exploring this option, there are still no definitive data on the optimal application for maximum therapeutic benefit.

In their critical review, the rationale for combining hypo-fractionated radiation with hyperthermia is presented. They discuss previous efforts and necessary steps to establish this combination as a clinically effective cancer treatment option.

The concept of employing hypo-fractionated radiation, which involves a reduced number of radiation fractions with larger absorbed doses, in combination with hyperthermia, offers several advantages over conventional radiation therapy. Reducing the total number of treatments clearly enhances cost-effectiveness; in addition, it would also make the entire treatment session more comfortable for patients (Sinha et al., 2024).

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

High overall response rates with complete remissions were achieved even in large tumours after application of non-contact, thermography-controlled water-filtered infrared superficial hyperthermia (wIRA), immediately followed by ultra-hypo-fractionated low-dose re-irradiation, consisting of 4 Gy once a week up to a total dose of 20 Gy (i.e. Intermittent Radiotherapy).

Effective tumour control in patients suffering from inoperable locally recurrent breast cancer (LRBC) in previously irradiated areas with total absorbed doses of 60–66 Gy can thus be successfully re-treated with Intermittent Low-Dose Irradiation (4 Gy) in combination with superficial hyperthermia.

However, the 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).

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

The size classification proves to be feasible, allowing for the assessment of the benefits and limitations of combining HT+RT in the treatment of different tumour sizes. It also improves the comparability of data and the stratification of prognosis groups, which helps to guide the decision between the curative and palliative aim of the treatment.

Using his classification, the retrospective analysis of 201 patients treated for 5 weeks with non-contact, thermography-guided hyperthermia (wIRA-HT) immediately followed by intermittent radiotherapy with 4 Gy, once a week, results in a high clinical overall response rate and a satisfactory local control rate, even in large tumours of LRBC. Low toxicity allows repeated reirradiation in case of new relapses.

The tumour response rate for complete remissions (CR rate) decreased with increasing tumour extent:

76% in rClass I, tumour extent < 100 cm^2

61% in rClass II, tumour extent >100 cm^2

36% in rClass III. II + tumour on contralateral chest wall or abdominal wall

1 CR in rClass IV. III + tumour on the back.

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

The *objective tumour response* rate OR (CR + PR) was:

100% in rClass I and
97% in rClass II,
97% in rClass III,
85% in rClass IV (Notter et al., 2020).

2.2 Intermittent Radiation Therapy and Anti-PD1 Immunotherapy

Head and Neck Cancer

Koukourakis and colleagues presented a clinical trial in 2023 of patients with locoregional recurrence of head and neck cancer, who were treated with anti-PD-1 immunotherapy and intermittent radiotherapy (iRIT) (Koukourakis et al., 2023a).

The study included 17 patients who, after conventional radiotherapy and chemotherapy, had recurrent inoperable squamous cell carcinoma of the head and neck region (HNSCC), as well as one patient with melanoma. They evaluated the efficacy and tolerability of Ultra-Hypo-Fractional Immuno-Radiotherapy, which in this case is analogous to Intermittent Radio-Immunotherapy (iRIT),

7 patients received only one fraction of 8 Gy to the tumour.

7 patients received 2 fractions of 8 Gy to the tumour, one week apart.

4 patients received 3 fractions of 8 Gy to the tumour, with a one-week interval

Nivolumab anti-PD1 immunotherapy was administered simultaneously with radiotherapy and then for a maximum of 24 cycles, until tumour progression or manifestation of immune-related adverse events (irAEs) occurred.

Taking into account the available preclinical experimental data (Koukourakis et al., 2023b), they assumed that 3 fractions of radiotherapy of 8 Gy with one fraction per week is optimal. However, to induce interferon type I response and improve the effectiveness of the treatment, it was shown that even a single fraction had a significant effect.

In the current study, a group of cancer patients who had recurrent inoperable head and neck tumours after previous conventional radiotherapy and chemotherapy were treated.

The patients were re-treated in three cohorts with 1, 2 or 3 fractions of 8 Gy with one fraction per week, in combination with *Nivolumab* anti-PD1 immunotherapy. Early and late radiotherapy toxicities were minimal, and immunotherapy also showed acceptable tolerance, with only three patients discontinuing immunotherapy.

The proportion of patients with "*Objective Response*" OR is the sum of the proportion with complete remission CR) and the proportion with partial response PR.

- After administration of only one radiation fraction of 8 Gy together with *Nivolumab* anti-PD1 immunotherapy, the OR was noted to be 57%.
- In patients who received radiotherapy with 2 or 3 fractions of 8 Gy, the OR was over 80%.
- In the current study the mean response rate OR was 70.6%, and 41.2% had complete remissions CR.

Most responders showed an increase in peripheral lymphocyte counts. The median time to tumour progression was 10 months. The 3-year predicted locoregional progression-free survival was 35%, while the 3-year disease-specific overall survival was 50%.

In conclusion, the study demonstrates that Intermittent Radiotherapy at 8 Gy per week, combined with anti-PD1 immunotherapy, yields high objective response rates and increased disease-free survival, which justifies further clinical trials with iRIT (Koukourakis et al., 2023a).

Non-Small Cell Lung Cancer (NSCLC)

Filippatos, and colleagues reported in 2023 the results of Ultra-Hypo-Fractional reirradiation of 8 Gy combined with anti-PD-1 immunotherapy in patients who had relapsed with locally recurrent non-small cell lung cancer after conventional radical chemo-radiotherapy (Filippatos et al., 2023).

The study included a cohort of 11 patients with locoregional relapses of non-small cell lung cancer (NSCLC) after radical chemo-radiotherapy. Between 2019 and 2021, these patients were treated weekly with one or two fractions of Ultra-Hypo-Fractional radiotherapy of 8 Gy and concomitant administration of anti-PD-1 immunotherapy (*Nivolumab* or *Pembrolizumab*).

The response rate of complete remissions (CR) was 27.2%, while the partial tumour regression (PR) was 54.6%, with more than 80% reduction of initial tumour dimensions. The objective response rate (OR) was 81.8% for this treatment with Intermittent Radiotherapy combined with Anti-PD1 immunotherapy.

The rate of patients free from relapse after 22 months was 54.5%, while the estimated 2-year disease-specific overall survival was 62%. These encouraging results justify the continuation of clinical trials of intermittent radioimmunotherapy (iRIT) combined with weekly radiotherapy in this group of NSCLC patients.

Radiotherapy-related toxicities were negligible, while immune-related side effects forced discontinuation of immunotherapy in 36% of patients, but the results were independent of PD-L1 status.

Their observations warrant further evaluation of ultra-hypo-radiotherapy with intermittent 4-8 Gy fractions and reduced immunotherapy dose administration to reduce side effects of immune intolerance (note BRP)

The results of this study provide encouraging evidence that radiotherapy with one or two 8 Gy fractions is feasible and can be safely combined with anti-PD-1 immunotherapy.

Despite the small number of patients, the significant tumour regression achieved and the long-term control with overall progression-free intervals, provide a basis for continuing trials of Intermittent-Radio-Immuno-Therapy in this group of NSCLC patients with poor prognosis (Filippatos et al., 2023).

Summary of clinical iRIT

Head and neck cancer patients with recurrent inoperable disease after prior conventional radiotherapy and chemotherapy can be re-treated with 1, 2 or 3 fractions of Intermittent Radiotherapy (iRT) of 8 Gy with one fraction per week in combination with *Nivolumab* anti-PD1 immunotherapy (iRIT). Early and late radiotherapy toxicities were minimal and the immunotherapy also showed acceptable tolerance, with only three patients discontinuing immunotherapy. In patients who received anti-PD1 immunotherapy treatment in combination with 2–3 fractions of iRT of 8 Gy, the objective tumour response rate was over 80%, and after only a single 8 Gy fraction of radiation, an objective tumour response OR of 57% was noted.

In conclusion, the study shows that patients with locally recurrent non-small cell lung cancer after conventional radical chemo-radiotherapy can be treated with anti-PD-1 immunotherapy in combination with one or two 8 Gy fractions (Filippatos et al., 2023).

The response rate of complete remissions CR was 27.2%, while the partial tumour regression PR was 54.6% with more than 80% reduction of initial tumour dimensions. The result of this iRIT regimen gave objective response rates of OR=81.8%.

2.4 Ultra-Hypo-Fractional Radiation Therapy Only

Astrid Persson and colleagues presented the 10-year results of a randomised phase III study at ESTRO 2024 in Gothenburg. They compared *Ultra-Hypo-Fractionated* (UHF), and *Conventionally Fractionated* (CF) radiotherapy (RT) in localised prostate cancer (PCa).

The results of UHF-RT were non-inferior to CF-RT in terms of symptom-free survival, with similar rates of late toxicities (Persson et al., 2024).

This large phase III clinical trial included 1200 men with localized prostate cancer at intermediate to high risk (Widmark et al., 2019):

Participants were randomized into two equal groups to receive either Ultra-Hypo-fractionated radiotherapy UHF-RT or Standard radiotherapy CF-RT according to:_

UHF-RT:

42.7 gray (Gy) administered in 7 sessions over 2.5 weeks
i.e. 6.1 Gy per fraction on days 1-3-5--8-10-12--15

Standard radiotherapy CF-RT:

78.0 Gy administered in 2 Gy per fraction over 39 sessions
i.e. daily for 5 days per week for 8 weeks

The researchers assessed 10-year survival, cancer recurrence, and treatment-related side effects, including urinary and bowel symptoms.

They compared potentially RT-related medically significant genital-urinary (GU) and gastrointestinal (GI) events, as well as mortality associated with these conditions, between the study groups using routinely collected health registry data in Sweden. They also compared the results with a population-based control group.

The main results at 10 years after radiotherapy were:

- Symptom-free survival (no recurrence of cancer or need for further treatment) was: 72% in the 2.5-week UHF-RT group compared with 65% in the 8-week standard CF-RT group.
- Overall survival: 81% for UHF-RT compared with 79% for standard CF-RT
- Prostate cancer-specific mortality: 4% in both groups
- Side effects: Urinary and bowel symptoms were mild to moderate in both groups,

Thellenberg-Karlsson, MD, PhD, of Umeå University, who presented the results at the ESTRO meeting added:

"*These results confirm that Ultra-Hypo-Fractional radiotherapy does not increase long-term side effects and provides as durable cancer control as conventional radiotherapy*"

Guckenberger commented that Prostate cancer is one of the most common cancers in men, and radiotherapy remains a necessary treatment. These results demonstrate how the development of radiotherapy methods can enhance the treatment's effectiveness, accessibility, and patient-friendliness, without compromising efficacy or safety. "Shorter treatment schedules mean that patients can return to their normal lives more quickly" (Guckenberger, 2025)

The results also indicate that further development of the fractionation pattern with intermittent irradiation, using either two or one fraction per week in combination with immunotherapy or hyperthermia between individual radiation fractions, has the potential to improve outcomes further and reduce the number of fractions (Persson, 2025a, 2025b).

2.5 Summary of Results with Different Treatment Regimens

Tabell 2-1 Summary of the Results of Different Treatment Regimens

Target	R	D	T	X	CR%	Ref.
Breast Ca Recidive <100 cm^2	5	4	7	wIRA	76	1
Breast Ca Recidive >100 cm^2	5	4	7	wIRA	50	1
Head and Neck SCC recidive	3	8	7	PD-1	50	2
Lung recidive NSLC	2	8	7	PD-1	27	3
Prostate primary UHFRT	7	6	1,4*	HFRT	65	4
Prostate primary Conv.RT	39	2	0,3*	CF	72	4
Breast Ca Recidive RT+HT	15	2	0,3*	mwHT	71	5

R: Number of RT fractions
D: Absorbed dose (Gy) per RT fraction
T: Time interval between RT fractions (* estimated mean)
X: Type of additional treatment between and after RT fractions
CR%: Treatment outcome: Percentage of complete remissions, Symptom-free survival
wIRA : Water-filtered infrared superficial hyperthermia ()
PD-1 : Anti-PD1 immunotherapy
mwHT : Microwave induced hyperthermia

Ref. : References

1. (Notter et al., 2020)
2. {Koukourakis, 2023 #178
3. {Filippatos, 2023 #72}
4. (Persson et al., 2024)
5 (Lindholm et al., 1995)

In summary, the results in Table 2-1 indicate that hyperthermia combined with radiotherapy provides treatment results that surpass the combination with immune checkpoint therapy. This motivates clinical studies of prostate cancer treatment with weekly intermittent radiotherapy with 6 Gy per fraction and hyperthermia. Perhaps 3 weeks of treatment is sufficient for a high rate of complete remissions. There is already clinical equipment for transurethral microwave-induced hyperthermia used for the treatment of benign prostatic hyperplasia.

There is also extensive clinical experience with deep hyperthermia in combination with radiotherapy in Switzerland, and an active development of new advanced methods for deep hyperthermia in Gothenburg (Stutz et al., 2022, De Lazzari et al., 2024).

Perhaps the combination with Intermittent Radiotherapy could offer a renaissance for the hyperthermia treatment. With a combination of intermittent radiotherapy and hyperthermia treatment, one can avoid the high costs and side effects of checkpoint immunotherapy, and additionally, extra radiotherapy capacity would be freed up at the radiotherapy clinics.

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Chapter III
Epilogue

3.1 Future development

Intermittent-Radio-Therapy (iRT) involves radiotherapy with a number of R fractions of ionising radiation, each with absorbed doses between 4 and 10 Gy delivered in time intervals T of 2 to 7 days or longer.

The primary mechanism of Intermittent Radiotherapy is that a single radiation fraction releases tumour antigens from tumour cells, and reduces the tumour's population of "Monolytic Derived Suppressor Cells" (MDSC), which increases the immunoactivity of the $CD8^{+}$T-cells (CTLs) killing tumour cells.

In addition, time intervals of 2-7 days between single fractions of radiation provide an opportunity for of CD8+ T cells (CTLs) to develop, and attacking living tumour cells.

During the time intervals between radiation fractions, vaccines, immune checkpoint antibodies, or other immunostimulating drugs or treatments can also be administered (Persson, 2025).

However, for different types of tumours, clinical studies are required to optimize the number of fractions R, radiation doses D, time intervals T and additional kind of treatment X. This opens up great opportunities to adapt the treatment to the type of tumour and individual in question by varying D radiation dose per fraction, number of fractions R, time interval T and additional treatment X,

According to available clinical studies, a common mean for Intermittent radiotherapy is R=3 fractions with 8 Gy per fraction and time interval T=7 days in combination with Immunotherapy type Anti-PD-1, which is able to give complete remissions in the treatment of Head and Neck tumour recurrence (Koukourakis et al., 2023).

With Hyperthermia as an additional treatment, the information is still sparse and requires more clinical studies. However, with a fraction dose of 6 Gy used in UHFRT treatment of the prostate, it could be a good start to study the possibility of reducing the number of radiation fractions by applying hyperthermia as an additional treatment in iRHT.

Standard primary treatment

- Primary surgery
- Postoperative conventional radiotherapy

Tumour recurrence after primary conventional treatment can be treated with Intermittent Radiotherapy iRT.

Intermittent Radiation Therapy

Fractionation dose D (Gy)

8 Gy(Teng et al., 2023, Koukourakis et al., 2023)

6 Gy(Widmark et al., 2019)

4 Gy (Newcomb et al., 2006, Notter et al., 2020).

Number of fractions R

1, 2, or 3 (Koukourakis et al., 2023)

Timeintervall T (days)

2 days (Newcomb et al., 2006)

7 days (Koukourakis et al., 2023, Notter et al., 2020).

Extra additional treatment X between radiation fractions

- **Immunotherapy** with Anti-PD-1 drugs administered before and immediately after Intermittent Radiation Therapy and continued for up to 24 cycles, until disease progression or manifestation of immune-related adverse events (irAEs) occurs (Koukourakis et al., 2023).

This means tremendous flexibility regarding the type and location of the tumour and the patient's status. Immunotherapy can be prescribed in a separate protocol, which includes the doses, number of treatments, and the administration schedule.

- **Hyperthermia** combined with radiation therapy provides treatment results that surpass the combination with immune checkpoint therapy, as shown in Table 2-1. High overall response rates with complete remissions were achieved using superficial hyperthermia (wIRA), followed immediately by Intermittent low-dose reirradiation, consisting of 4 Gy administered once a week for 5 weeks.

This motivates clinical studies of primary prostate cancer treatment with weekly intermittent radiotherapy with 6 Gy per fraction and hyperthermia. Perhaps 3 weeks of treatment are sufficient to obtain complete remissions. There is already clinical equipment for trans-urethral microwave induced hyperthermia available, used in the treatment of benign prostatic hyperplasia.

There is also extensive clinical experience of deep hyperthermia in combination with radiotherapy in Switzerland, and an active development of new advanced methods for deep hyperthermia in Gothenburg (Stutz et al., 2022, De Lazzari et al., 2024).

Perhaps the combination with intermittent radiotherapy could offer a renaissance for the hyperthermia treatment? With hyperthermia treatment, one would avoid the high costs and side effects of checkpoint immunotherapy. Additionally, the radiotherapy clinics would gain extra capacity.

Tumour recurrence after primary conventional treatment can be retreated with Intermittent Radiotherapy in combination with ImmunoTherapy and/or Hyperthermia.

To stimulate interest in Intermittent Radiation Therapy, a "Workshop" should be arranged entitled:

Intermittent-Radio-Therapy,–Immunotherapy, and Hyperthermia

Clinical researchers with experience in immunotherapy and radiotherapy and hyperthermia should be invited.

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I would also like to thank the researchers, Silvia Formenti and Sandra Demaria, for their enthusiastic assistance in getting the Lund results published in the scientific journal Radiation Research.

I would also like to express my admiration and enthusiasm for the therapeutic results of Notter and colleagues' combining infrared-induced hyperthermia (wIRA) and Ultra-Hypo-Fractionated re-irradiation in the treatment of breast cancer recurrence.

Finally, I would like to express my great admiration for Dr. Michael I. Koukourakis and colleagues' clinical studies in Greece, who have shown that Intermittent radiotherapy with 8 Gy in combination with Anti-PD1 Immuno-Therapy works as a clinical treatment for relapse from conventionally treated Head-Neck and Lung tumours.

Their results have prompted me to present this story, with the hope that more clinicians will be motivated to further evaluate intermittent radiotherapy in combination with Immunotherapy and/or Hyperthermia as therapeutic options for patients who relapse after undergoing conventional radiotherapy.

Based on the positive results of the 10-year evaluation of prostate cancer, it might be worth performing a clinical evaluation of primary Intermittent radiotherapy in combination with intra-urethral hyperthermia.

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A story of a Royal Meeting that created Intermittent Radio Therapy (iRT)

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This story has its origin in my presentation at the 1983 Research Day in Lund, to HM King XIV Gustav on our development of microwave-induced hyperthermia treatment of breast cancer recurrence, which brought me together with Professor Leif G. Salford, whose presentation was next to mine.

Shortly before the turn of the millennium, Leif Salford initiated a clinical trial "*Brain Immune Gene Tumour Therapy" (BRIGTT)*. A specific tumour vaccine was produced based on tumour cells that he extracted from the tumour tissue of the glioma patient he had previously operated on. My participation contributed to the radiation sterilisation of the vaccine before it was administered to the patients. The survival time of the patients treated with the vaccine was prolonged but none recovered completely.

In an attempt to enhance the effect of vaccination by exploiting the experiences with combining radiotherapy with hyperthermia, I utilised the tumour model previously used in the preclinical tumour-immunological research that formed the basis for Salford's clinical vaccination trial *BRIGTT* with malignant gliomas.

A vaccine of syngenetic N32-Tumour cells was combined with radiotherapy of Fischer-344 rats with N29 glioma tumours inoculated into the brain, and the results showed that:

- Radiation therapy alone with 5 Gy did not result in any survivors.
- **In contrast, if immunotherapy with 3 rounds of vaccine was combined with only one fraction of 5 Gy radiation therapy, six out of eight treated animals survived (approx. 75%).**

This unexpectedly positive result for a previously incurable cancer spurred me to try to advocate for a new tumoural treatment regimen with intermittent radiation therapy in only a few low-dose fractions in combination with immunotherapy. However, shortly after the first results were presented in 2003 at a Neuro Oncology Congress in the USA, I retired and the project was not given any resources to develop further.

But after 20 years, clinical studies have been reported showing that intermittent radiation therapy combined with infrared-induced hyperthermia gives good results in the treatment of breast cancer recurrence. Similar results obtained in Lund with microwave-induced hyperthermia in the 1980s-90s.

Furthermore, immunotherapy in combination with intermittent radiotherapy of 8 Gy works effectively with immune checkpoint inhibitors, which are used to block CTLA-4 and/or PD-1, thereby allowing the killer cells, specifically cytotoxic T-lymphocytes (CTLs), to eliminate cancer cells.

I hope that the story will motivate further clinical evaluation of intermittent radiotherapy in combination with immunotherapy and/or hyperthermia as a therapeutic option for patients with recurrent cancer after undergoing conventional treatment regimens, and based on the positive results of the 10-year evaluation of prostate cancer, also as primary treatment.