Challenges and Solutions of Oncological Hyperthermia

Challenges and Solutions of Oncological Hyperthermia

Edited by

Andras Szasz

Cambridge
Scholars
Publishing

Challenges and Solutions of Oncological Hyperthermia

Edited by Andras Szasz

This book first published 2020

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-4817-1
ISBN (13): 978-1-5275-4817-6

TABLE OF CONTENTS

PREFACE

Hyperthermia in oncology has its roots in ancient medicine. Medical processes using heat constituted the very first curing approach, remaining a vital "household remedy" even nowadays. The heat from sunlight is also well-accepted as a universal support of health, and the biological effects of the Sun (natural, organic vegetation, vitamin supports for human, etc.) are essential for our healthy living. The first written description of the application of heat in oncology was made by Hippocrates, the "founding father" of European medicine. He knew the simple rule of the roots of medicine well: do not treat a disease of an individual but an individual with a disease. He knew the enormous complexity of the human being and its complex interactions with the environment well, and he applies this unique knowledge to win the war against cancer. From that time, tremendous heat-therapy approaches had been explained for, and applied to the curing of cancer, but the real breakthrough was the appearance of electromagnetism in medicine. Since that time, numerous medical applications have been described, and a considerable number of books have collected the updated knowledge.

Life is based on energetically open systems, where environmental conditions determine their equilibrium. The living system is controlled complexly, forming homeostasis. Diseases break the relative equilibrium and risk the relative stability of the system. The human body tries to reestablish homeostasis in many ways by enhancing negative feedback controls. Multiple actions of the human physiology try to compensate and correct the damage caused by diseases. To cure a disease, most medical approaches act by changing conditions (diets, medicaments, other supplies) to try and restore the body back to the previously working equilibrium. However, in many cases, this works against the natural homeostasis; the constraining action induces new negative feedbacks from the living object. The living organism starts to fight against our constraints together with fighting against the disease itself. This is the problem of classical hyperthermia, which introduces a new constraining effect: the termination of the natural homeostasis by heating. This constraint induces new physiological feedbacks forcing the body to fight on a "double front": against the disease and the "healing" action. Our task, in well-developed

oncological hyperthermia, is to help the system in the fight against the malignancy, providing as much support as possible for the healing processes.

The present book is a unique continuation of the broad set of existing publications, concentrating on the complex means of helping the natural processes to fight against cancer. This book collects together articles presented at the 36th annual conference of the International Clinical Hyperthermia Society (ICHS), held in Budapest in September 2018. The speciality of the conference is its unique approach to the topic. The concept of this goes back to the roots, to the natural radiation of the Sun. The radiation of the Sun has well-recognizable effects: the heating and electromagnetic effects that develop life and support all living phenomena. Heat energy ensures the relatively narrow but stable temperature window of the human body and its environment. The heat (and its consequence, the temperature) alone would not be enough to understand the essence of life. The bioelectromagnetic excitation of electrons by the Sun creates life on our globe. As the Nobel Prize-winning physiologist Albert Szent-Györgyi stated: “Life is nothing but an electron looking for a place to rest”. All chemical reactions that construct such complex structures as living objects are based on the electron-excitation of the Sun, which excites the electrons by photo-conversation and keeps the proton-pumping loop active. At the end of the day, the process produces carbohydrates, which are massively used as an energy-source by animals (see figure 1). When the electron finds “its rest” that is the only equilibrium, electrons wiping out life and destroying all life processes when the excitation is too high and the system is not able to use the excess energy. The optimal energy of electrons in a specific range of energy is life. It is unquestionable that these effects, heating-supported temperature conditions and bioelectromagnetic excitations, are both essential for proper living conditions.

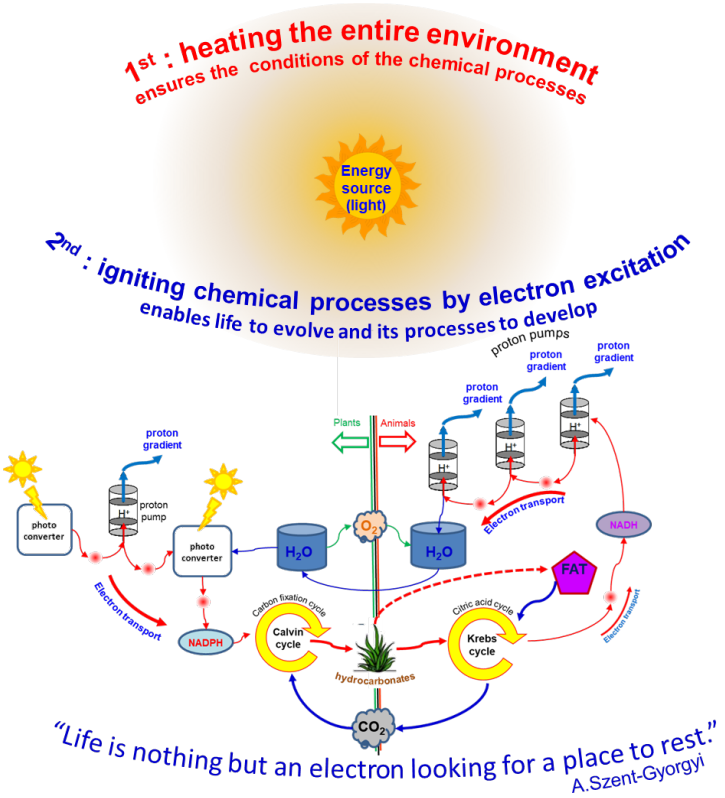

Figure 1. The complex ecology created by the radiation of the Sun. Electron-transport drives the chemical processes of the living ecosystem. The Sun provides appropriate and, at-the-roots, sole-source thermal conditions with heat and bioelectromagnetic effects. The general heating fixes the environmental and individual bio-system temperature for optimal chemical reactions.

We face the same problem with hyperthermia in oncology: heat energy fixes the conditions where bioelectromagnetic interactions guide the chemical reactions, support the normal networking processes and eliminate disorders like malignancy in the system (see figure 2). This double effect of the applied electromagnetic fields (heating and modifying chemical processes) was the subject of the conference and gave a unique purpose for this book.

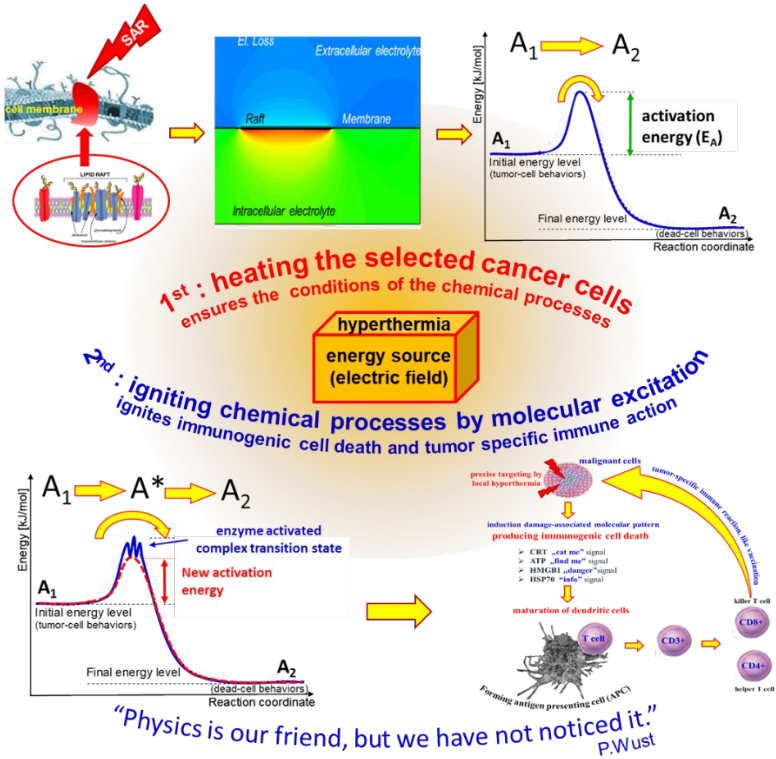

Figure 2. The double task of the precise, cellularly selective targeting of energy.

Heating increases the temperature of the target and allows the application of the Arrhenius principle to determine the rates of chemical reactions. Well-localized precise heating does heat homogeneously, but it creates a selection while targeting the malignant cells, exciting the lipid rafts of the cellular membrane. The field-effect modifies the transition state of the molecules, exciting extrinsic signals to intracellular changes. The well-regulated signal pathway could produce a damage-associated molecular pattern (DAMP), promoting immunogenic cell death (ICD). This process could give genetic information for dendritic cells and mature them, forming an antigen presentation situation (APC formation) which develops killer and helper T-cells, resulting in a tumour-specific immune reaction. The heating process has various biophysical/medical effects, having pros and cons for the eliminating of the malignancy (see figure 3).

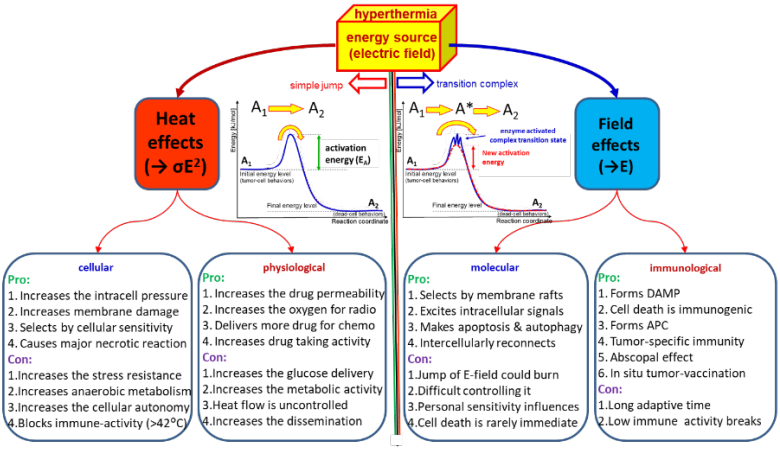

Figure 3. The two effects of well-controlled hyperthermia: the heating which depends on the square of the electric field vector and the field-effect which linearly depends on the field. The pro and contra effects are listed in various categories of the hyperthermic action.

The book follows the structure of the conference, except in some of the papers having been presented elsewhere. The fundamental message of the meeting was focused on the clinical results of a special kind of hyperthermia, modulated electro-hyperthermia (mEHT). The presentations show the results from planning to combined therapies for various cancer types, such as advanced cervix carcinoma, pancreatic cancer, glioblastoma, and triple-negative breast cancer. One of the compelling topics was centred on immune-oncology, including the abscopal effect, which transforms this local therapy to a systemic one, treating the distant micro- and macro-metastases by targeting the primary tumour alone. There was special emphasis on the fact that integrative medicine is showing excellent clinical outcomes with natural supportive therapies in a wide range of cancer types. The prospective double-arm study using high-dose intravenous vitamin C combined with mEHT for non-small cell lung carcinoma showed remarkable results. The technical status of hyperthermia, including the explanation of modulation together with multiple molecular research in the topic, closed the intensive work of the conference.

R. Nixon, a former president of the United States, declared war against cancer in 1971. From that time on, tremendous efforts have been made in the “pitched battle”, but the fight has led to a state of stabilized warfare rather than a hands-down win. There are multiple reasons for the lack of

success, and probably a change of paradigm is necessary to move forward – this book is devoted to moving towards this goal.

Andras Szasz, PhD
Professor of physics & biophysics
Head, Biotechnics Department, St Istvan University Hungary
Editor of the present book

CHAPTER 1

CHALLENGES ASSOCIATED WITH HYPERTHERMIA

CARRIE MINNAAR

MSc PhD Rad onc/Radiobiology

Hyperthermia has been around in oncology for decades. Early results were promising but were followed by challenges which led to clinicians abandoning the field. These challenges are discussed in detail in the following pages and include: high costs and limited reimbursement; technical and logistical complexities; challenges of homogenous heating; temperature monitoring; defining the thermal dose goals; quality assurance [1], [2], [3]; lack of standardisation [2]; and poor focusing and selective heating [4], [5]. The lack of awareness, availability, and financial resources [6] in the field of hyperthermia are also challenges which must be overcome in order to grow the field effectively.

Such challenges are expected when a new field is proposed for inclusion into standard protocols, and any developing field has obstacles which must be overcome before it can be accepted into standard clinical practices. Current views on hyperthermia in oncology lack the agreement of the users and manufacturers on techniques, protocols, dose measurements, and safety, and this had led to inconsistency in the results. The biological effects of hyperthermia have been widely described in pre-clinical studies; however there are many effects which are still not fully understood. This has left users with questions regarding the optimal timing and protocols for the combining of hyperthermia with chemotherapy or radiotherapy. Without a standardised approach to the hyperthermia treatments, the acceptance and reimbursement of hyperthermia becomes a complex debate. There are strong opposing opinions resulting in divisions in the hyperthermia community, a fact which causes confusion amongst users regarding optimal treatments. The development of a new field with such

promising results should be approached with enthusiasm, scientific rigor, and the formulation of clinical trials in order to answer the questions that the field of hyperthermia is still faced with. In this chapter, we hope not only to highlight the challenges but also to draw attention to the research questions which need answering in order that these challenges can be overcome, enabling clinicians to implement hyperthermia in their standard practices with confidence and with reliable clinical outcomes and reproducible results.

Economic Considerations

Accessibility to treatment is an obvious challenge that all new treatments must overcome. In the face of rising drug costs, mostly due to the increased research and development required for the more complex compounds, affordability plays a major role in accessibility. In 2017 the World Health Organisation compiled a document on the priority medical devices required for cancer management. The document grouped medical devices into the following categories: vaccination, clinical assessment, and endoscopy; medical imaging and nuclear medicine; surgery; clinical laboratory and pathology; radiotherapy; systemic therapy; and palliative care and end-of-life care. According to the document, more than 50% of new cancer cases require radiotherapy as their definitive or adjuvant therapy. Radiation devices used for external beam radiation include linear accelerators and, in less developed regions, Cobalt 60 units. These devices can cost millions of Euros, and the installation and use of the devices require specialised facilities and skilled staff. The treatments are labour intensive and complex, including planning, monitoring, and follow-ups; however, given the essential nature of the treatments, there is a strong international drive to increase accessibility to radiotherapy treatments [7].

Heating the tumours has shown benefit in sensitising tumours to treatments and in improving outcomes, especially in tumours known to be resistant to radiotherapy. The improved sensitisation to radiotherapy is largely attributed to the enhanced perfusion and improved tumour oxygenation resulting from the localised heating [2] and to the inhibition of protein synthesis and DNA and RNA repair mechanisms [8], [9]. The chemo-sensitisation process is driven by increased drug accumulation due to the increased perfusion, abrogation of cell cycling in the S-phase of cell division, and the potential for the reversal of drug resistance [2]. These mechanisms are discussed elsewhere in the literature. While hyperthermia is known to improve clinical outcomes in several tumour types [10], the

hyperthermia devices are not considered priority medical devices and hyperthermia is not likely to be curative as a stand-alone therapy.

Reimbursement

The high costs of some hyperthermia technologies and the non-essential status of the treatments in the management of cancer make it difficult, in regard of the cost versus the benefit, to motivate the addition of hyperthermia to standard treatment protocols outside of a research setting. The treatments are labour intensive, and patients require constant monitoring [11]. The duration of treatment can be several hours, including recovery time. The cost to benefit ratio plays a crucial role in the affordability, accessibility, and therefore acceptance of hyperthermia. Despite these costs, Van der Zee et al. showed a maximum discounted cost-per-life-year-gained of 3,956 Euros in their study on the treatment of locally advanced cervical cancer with or without hyperthermia (using the electromagnetic wave-guided technology) in academic research facilities in the Netherlands [12]. Roussakow assessed the efficacy and cost-effectiveness of modulated electro-hyperthermia concurrent with dose-dense temozolomide on a 21/28 day regimen compared to temozolomide 21/28 days alone in patients with recurrent glioblastoma. The results suggested that modulated electro-hyperthermia significantly improves the survival of patients receiving the temozolomide 21/28 day regimen and the economic evaluation suggests that the combination therapy is cost-effective and results in a saving [13]. Health insurance companies need to be made aware of these cost benefits, and an increased output of publications on the topic would further assist in motivating reimbursement.

The capital investment for a hyperthermia device depends on the technology used, and ranges from a hundred thousand Euros to a few million Euros, with some hyperthermia devices costing in the same price range as linear accelerators. The treatment time and facilities required (e.g. shielding, operating theatre, recovery room, imaging studies) add to the cost of each treatment. The complexity of certain forms of hyperthermia treatment requires specialised training for clinicians and medical physicists in order to develop, plan, and apply the treatment. This requires dedicated clinicians with a specific interest in hyperthermia, and the labour-intensive work and highly skilled staff required to perform the work further increases the cost-per-treatment. Unless the treatments are reimbursed or administered in an academic or research setting, and depending on the type of hyperthermia administered, patients may not be

able to afford the treatments. Without being able to bill sufficiently, administering the treatments is not economically viable for clinicians and clinics [3]. These costs have been cited as a major inhibiting factor to the widespread availability of the treatments around the world in developed and resource-constrained settings [14].

A confounding factor in the discussion on the reimbursement of hyperthermia treatments is the variation in costs between different techniques. In some countries, health insurance companies differentiate between capacitive and radiative hyperthermia techniques and offer different reimbursement rates for each technique. However, in countries where hyperthermia is not established well, there is still confusion and doubt regarding which technique is best suited to the regions' needs. Only a few tumour locations are approved for reimbursement around the world. The most established tumour locations for hyperthermia treatment at the moment include locally advanced cervical cancer [15], [16], local chest wall recurrences in breast cancer patients [17], [18], high risk soft tissue sarcomas [19], [20], pancreatic cancer [21], bladder cancer [22], head and neck cancer [23], melanoma [24], and brain tumours [25], [26]. As the body of literature grows, we are likely to see more tumour types and locations being approved for reimbursement. Until then, the majority of patients are left having to pay for their treatments, which, depending on the type of hyperthermia used, can range from 250 Euros to over 3,000 Euros per treatment.

Accessibility

The cost and resources required for the treatments have had a particularly large impact in countries such as the USA which has historically relied on complex systems to administer treatments and in which reimbursement is limited [3]. With the exception of a handful of research institutes in countries such as the Netherlands, Switzerland, and Germany, there is a general lack of funding internationally for further research to broaden the scope of applications, to investigate newer and more affordable technologies, and to better define the temperature and heating goals. Countries relying on the complex systems may, therefore, find it difficult to improve accessibility to the treatment. Regions, in which the technology is locally manufactured and more affordable, such as Asia [27] and some European countries, are able to offer hyperthermia at a more affordable price and hyperthermia is, therefore, more frequently added to the basket of oncology treatments offered to patients.

Access to hyperthermia in low-to-middle-income countries is limited. At the time of publication, there is only one centre in Sub-Saharan Africa offering hyperthermia treatments. In recognition of the need for less costly and more practical, simpler techniques, methods to calculate treatment doses without using magnetic resonance (MR) monitoring or intratumoural probes, have been proposed. Capacitive heating offers a more affordable heating solution which does not require the same time and resources to administer the treatment. The advantages and disadvantages of various heating technologies are listed in Table 2. Szasz proposed a selective heating method which measures the dose by the energy applied and not by the measured temperature [28], reducing the treatment costs further. A South African research group investigated the use of this technique on high risk (including HIV-positive) locally advanced cervical cancer patients in a setting where staff, funding, and facilities were limited. The Phase III randomised controlled trial randomised 210 patients for treatment with either chemoradiotherapy alone or combined with two hyperthermia sessions a week. A capacitive heating system was used to achieve a very mild heating combined with an amplitude radiofrequency signal and low power output, also known as modulated electro-hyperthermia (mEHT). In a report on local disease control, the researchers analysed 101 participants treated with chemoradiotherapy and 101 participants treated with chemoradiotherapy combined with mEHT. Fifty-one percent of the participants were HIV-positive. The six-month local disease-free survival and local disease control at six months post-treatment were significantly higher in the hyperthermia group, 38.6% and 45.5% respectively, than in the control group, 19.8% and 24.1% respectively (p=0.003). The researchers reported clinical benefits to the addition of the hyperthermia technique, without a significant impact on the work-flow and resources required to treat the patients [14]. More affordable heating technologies such as this may help to overcome the affordability and accessibility challenges, especially in non-university settings and in countries with limited resources.

Funding

Patents in the pharmaceutical industry protect the companies' investments into the research and development of their products. Billions of dollars can, therefore, be spent annually on research in the pharmaceutical industry. The diversity of techniques which can be applied to heat tumours means that there is little protection of the hyperthermia manufactures' financial investments, even with patents. When combining

hyperthermia with chemotherapy, the research possibilities are endless, with a variety of chemotherapeutic agents, each responding differently under hyperthermic conditions [2], [29], [30], and the variety of drug combinations and protocols available. Trials investigating the addition of hyperthermia to various cytotoxic agents are expensive and time-consuming and not likely to be sponsored by pharmaceutical companies. The manufacturers of hyperthermia devices do not have the funds for large trials on various hyperthermia protocols and tumour locations combined with chemotherapy, radiotherapy, or the combination of chemoradiotherapy. Research in hyperthermia is, therefore, largely investigator-driven with researchers applying for funding grants to conduct the trials.

Research and Results

The result of the lack of funding for research is that many of the studies published are relatively small and often overlooked as the level of evidence is considered to be poor, despite the significant results. For example, Van der Horst et al. reviewed the literature on the use of hyperthermia for pancreatic cancer, and while the authors found that hyperthermia may be of benefit, the poor quality of the studies made it difficult to draw definitive conclusions [21]. In an analysis of publications available in 2008, Van der Zee et al. reported Level I evidence for the use of hyperthermia combined with radiotherapy for the management of head and neck tumours, melanomas, sarcomas, breast cancer, glioblastoma multiforme, bladder cancer, cervical cancer, rectal tumours, oesophageal tumours, and various superficial tumours. Level I evidence for the combination of hyperthermia and chemotherapy was reported for bladder, lung, and oesophageal tumours [6]. Since then, several more papers have been published with larger patient numbers and improved results. Most notably: re-irradiation combined with hyperthermia for the management of chest wall recurrences in breast cancer [18]; an update on ten-year survival in the study by Issels et al. on the use of neoadjuvant doxorubicin, ifosfamide, and etoposide either alone or in combination with hyperthermia for the management of soft tissue sarcomas [20]; and the use of capacitive heating combined with chemoradiotherapy for locally advanced cervical cancer [14]. The last-named study used a system with a self-selecting capability which allows dose measurement based on energy absorbed rather than temperature achieved. Datta et al. summarised the available research in 2015 and reported that the addition of hyperthermia to radiotherapy protocols resulted in improved outcomes with an odds ratio of around 2.3 [10].

There are numerous positively reported trials and meta-analyses showing the benefit of hyperthermia [10], [31], [32]. This chapter is dedicated to the challenges of hyperthermia and will, therefore, only discuss a few selected trials that highlighted these challenges and did not show significantly improved results with the addition of hyperthermia.

Table **1**Table 1 summarises the selected trials and challenges in the field, such as temperature relevance; dose measurement; and heating methods. The literature generally agrees that these studies lack proper thermometry, were unable to achieve the desired temperature, and made use of inappropriate or incorrect equipment [2], [11], [33], [34]. Some studies have even raised concerns regarding an increased risk of tumour dissemination following hyperthermia [35], [36], [37], [38].

Trial	Results	Author's comments	Criticism	General comments
Harima et al. (2016) CRT +/- HT (capacitive 8MHz heating) applied weekly (800–1500W) for LACC [39].	Primary end-point of 5-year survival did not show improvement with HT.	The average temperature was 41.1ºC ± 0.7ºC, (in radio- and/or chemo-sensitising range), the sample size was too small (n=101).	Capacitive heating is not able to heat up pelvic tumours [40]. Inadequate RT and thermometry. Underpowered.	Capacitive heating has shown to improve outcomes for LACC when combined with RT [41] and CRT (modulated EHT) [14].
Flameling et al., (2016) CRT +/- HT (radiative hyperthermia) for LACC [42].	CR and 5-year survival were not statistically different between both groups.	Study closed early due to slow recruitment.	Poor recruitment, variations in protocols.	Positive results seen with radiative HT + RT for LACC [16] and with capacitive (130W modulated mEHT) +CRT in LACC [14].
Vasanthan et al., 2005 RT +/- HT (capacitive 8MHz) 1/wk at 800–1500W for LACC. [38]	No benefit in local control or survival with the addition of HT to RT. Worse acute toxicity in the HT group.	High risk patients from a developing country. Tumour volumes may have been too large for hyperthermia.	Suboptimal RT; inadequate HT treatment delivery; and inadequate sample size [10].	Improved outcomes seen with capacitive + RT [41] and capacitive (130W modulated EHT) +CRT [14] for LACC.
Sharma et al., (1991) RT +/- HT for Stage II and III cervical cancer. HT delivered by intracavitary brachy-HT [43].	18-month local control rate: 50% after RT (11 out of 22) and 70% after RT+HT (14 out of 20).	Increased incidence of distant metastasis in HT+RT group (4 out of 23 cases) vs RT group (1 out of 23 cases) was noted.	The numbers of patients were too small to make the difference statistically significant [6].	Other heating methods have shown better results [14][41][44].
Emami et al., (1996) interstitial	No difference in any of the study endpoints was	Only 1 of 173 evaluable patients met the criteria of	Inadequate heat delivery [2][6].	Literature on interstitial heating is limited. Detailed

HT+RT vs interstitial RT for persistent /recurrent disease after RT or surgery [36].	noted; CR or 2-year survival.	a minimum 42.5ºC for 30–60min as defined by the protocol.		descriptions can be found in the QA guidelines by Trefná et al. [45].
Perez et al. (1991) RT +/- HT (wave-guided applicators at 915MHz) for superficial tumours [46].	No difference in response between groups; response in the HT group was related to tumour size (tumours <3cm responded better).	Inadequate heating, no thermal mapping, and the use of 915MHz instead of 433MHz contributed to poor results.	Inadequate heat delivery [6]; response in small tumours suggests if all tumours could be effectively heated, the response may be improved [2].	Significant improvement with HT+RT (433MHz microwave spiral strip applicators) for superficial tumours <3cm seen in other studies [47].
Kapp et al. (1990) RT+2HT vs RT+6HT. 70 patients, 179 treatment fields. Superficial recurrent/ metastatic tumours [48].	No significant differences in response at 3 weeks (p=0.89). Mean min, max, and avg. intra-tumoural temp.: 40.2°C, 44.8°C, 42.5°C, respectively.	Thermo-tolerance may be partially responsible for limiting the effectiveness of multiple closely spaced hyperthermia treatments.	Heating was not sufficient [6].	See comment above. Other heating techniques have shown positive results in superficial tumours [18].
Datta et al. (1990) RT +/- HT for head and neck cancers using 27.12MHz RF capacitive heating [49].	CR rate was 31% following RT and 55% following RT+HT. The difference was not significant.	No difference between groups with stages I and II disease. Larger difference seen in stages III and IV. Large tumours responded better in the HT group.	The numbers of patients were too small to make the difference statistically significant [6].	Overall, a benefit is seen with the addition of HT to RT for head and neck tumours [23].

Table 1: Trials highlighting challenges in hyperthermia

Abbreviations: Avg: average; CR: complete response; CRT: chemoradiotherapy; HT: hyperthermia; LACC: locally advanced cervical cancer; Min: minimum; Max: maximum; QA: quality assurance; Wk: week.

Protocol Design and Guidelines for Clinical Practice

Guidelines for the development of protocols for clinical trials in oncology are essential. This would allow the collection and comparison of various methods and outcomes which would benefit clinical practice and the future development of the field [50]. The challenges with developing protocols are the variety of devices on the market and the variety of heating mechanisms. For research protocols, temperature monitoring is still strongly recommended in order to determine the heating potential of the technology and the relationship between temperature and outcomes

[51]. Temperature monitoring, however, comes with its own challenges, as described later in this chapter. In response to the challenges of temperature monitoring, Szigeti et al. propose a different method of dose evaluation, based on applied energy, which could be personalised and more easily and uniformly applied in clinical practice [52].

Developing guidelines for clinical practice is as important as protocols for trials. In clinical trials, where there is potentially more funding, protocols could include more complex and expensive planning and the monitoring of treatments. However, the application in a clinical setting requires stream-lined and affordable technology that can be easily integrated into the workflow. In radiation oncology, guidelines for the application of radiation are often developed for each malignancy and recommendations are drawn from the vast number of studies published on each tumour type. In an analysis of global radiation therapy research, Aggarwal et al. analysed 62,550 radiation therapy research articles from between 2001 and 2015, from 127 countries in 2,531 journals [53]. This huge body of research dwarfs the body of research on hyperthermia.

With the relatively limited amount of research in the field of hyperthermia, there are still gaps in the knowledge needed to develop guidelines for some malignancies. Adding to the complexity of the task are the variety of devices and the variety of combinations with chemotherapy and radiotherapy. The field needs guidelines for tumour locations, tumour types, and combination therapies. While dosing and temperature guidelines are still being debated, research has provided us with some clarity regarding the timing of combination therapy. We know that the optimal timing of hyperthermia with chemotherapy or radiotherapy is either concurrent or that the administration of hyperthermia should be immediately after the administration of chemotherapy or radiotherapy [54]. We also know that when hyperthermia is administered after radiotherapy, preclinical evidence indicates that a shorter time interval between the two treatments is associated with a better outcome [55]. While this was confirmed in a small retrospective study on 58 cervical cancer patients [56], a larger retrospective analysis of 400 cervical cancer patients showed that administering hyperthermia up to four hours after external beam radiotherapy is not associated with worse outcomes [57]. Horsman and Overgaard report that the effect of heat as a radiosensitiser on healthy tissue decreases more rapidly when hyperthermia is given after radiotherapy compared with hyperthermia administered prior to radiotherapy [55]. It is also generally accepted that hyperthermia can be administered immediately before radiotherapy, and several studies have

used this protocol for logistical reasons with positive outcomes [14], [58]. Some authors have however raised concerns that hyperthermia administered before radiotherapy risks increasing the rate of dissemination and concerns such as these need to be confirmed in order to formulate guidelines [59].

The frequency of hyperthermia administration varies in the literature from weekly to daily treatments, and the temperatures achieved range from 39°C to more than 43°C. The temperature has not been associated with improved outcomes in all of the studies [60]. The same applies to the number of treatments. Franckena et al. showed [44], that the number of hyperthermia treatments emerged as a predictor of outcome for locally advanced cervical cancer [44], while Engin et al. [61] and Emami et al. [62] showed that the number of treatments did not affect the outcomes in their studies on superficial tumours [61], [62]. These discrepancies could be related to the tumour type, the heating technology [1], or the method of dose measurement [4].

Quality Assurance Guidelines

The development of quality assurance (QA) guidelines for hyperthermia is complex, due to the variety of techniques available. Quality assurance guidelines, therefore, need to be developed for each type of heating technique. The first QA guidelines to be published were developed by the Radiation Therapy Oncology Group in 1989. However, there were many gaps in the paper, and the authors acknowledged the lack of knowledge on standardisation in equipment, treatment procedures, patient monitoring, and treatment documentation [63].

In Europe, updated QA guidelines for regional hyperthermia were published in 1998 by the European Society for Hyperthermic Oncology (ESHO). These guidelines were cited as mandatory for all ESHO approved clinical trials and included treatment planning, treatment procedures, documentation, and equipment. Several new devices and technologies have been developed since the publication of these guidelines [64]. Bruggmoser et al. published an update in 2011; however, the guidelines were not inclusive of all technologies. In this report the authors describe the goal for an effective hyperthermia treatment as the application of the highest therapeutic temperature which is tolerable for the patient, but that it should not exceed 44ºC. The temperature goal in this statement is vague and does not provide guidance for the ideal temperature or the effect of temperature on outcomes. The goal for treatment time was, and is

still, widely understood to be 60 minutes. The paper deals specifically with phased array devices, which are used primarily in research and academic facilities. Unfortunately, the paper does not discuss devices which are more accessible and are therefore available in clinical practices [51]. The Hellenic Association of Medical Physicists (HAMP), in cooperation with the Hellenic Society of Oncologic Hyperthermia (HSOH) in Greece, published guidelines on superficial and deep hyperthermia systems. Unfortunately, these guidelines have similar problems in that they are not inclusive of all heating techniques and the guidelines cannot, therefore, be applied to all devices. In these guidelines the desired heating is in the range of 40 to 44°C [65], which does not differentiate between moderate heating and the historically high, but largely unachievable, temperatures of above 43°C.

In acknowledgement of the variety of heating methods, in 1991, the Radiation Therapy Oncology Group published three papers: one on deep heating techniques [66], one on interstitial heating [67], and one on ultrasound heating [68]. The challenge, however, is that each method has variations in the technology used to achieve the heating and the characteristics specific to each technology also need to be addressed.

The guidelines on interstitial hyperthermia were updated in 2019 [45]. In the most recent guidelines by Trefná et al. on superficial hyperthermia, published in 2018, it is recognised that there are often cases that cannot be heated and the guidelines propose identifying and excluding these patients from trials [69]. There is a drive towards personalised medicine in oncology where, for example, patients could be tested for radio- and chemo-resistance and, based on the results, excluded from treatments that may be ineffective. This is not yet standard in most clinical settings, and there is, therefore, still a risk with any treatment that the patient does not respond. Excluding patients from trials based on heating capability may result in inflated results which may not be fairly extrapolated to the general population in clinical practice where patients might not be evaluated for “heatability”. The temperature is still believed by many to be a crucial predictor of treatment response, despite many studies indicating that lower temperatures are also effective [30], [70], [71]. Some authors have indicated that the electrical energy, and not only the temperature, may also be involved in the response to the treatment [14], [33], [72]. The authors of the guidelines have included a variety of technologies and techniques [69]; however, not all of the devices are represented in the paper, likely due to the wideness of the variety of devices and the complexity of the task. As a result, there are some small discrepancies. For

example, in the guidelines, it is recommended that capacitive heating devices use saline in the water bolus in order to improve the impedance matching between the electrodes and the muscle tissue, and to spread the radiofrequency currents over the contact area, reducing skin burns at the edge of the electrode [69]. This is not always the case. In modulated electro-hyperthermia, which uses devices with a capacitive heating technology combined with an amplitude modulated frequency, distilled water is used in the water bolus. This is due to the reliance of the selectivity on the differences in biophysical properties, and therefore electrically neutral water is needed to reduce the interference with the conductivity and selection mechanisms.

Finally, researchers in the United States of America published guidelines in 2014 on the requirements of a hyperthermia clinic. However, these guidelines are broad and refer only to the requirements of the heating technologies available in the United States. These guidelines also addressed patient selection, as the heating methods used are considered only to be able to heat certain tumours [73].

There are too many variations in dose calculation, monitoring, administration, and planning between the various technologies for one guideline to be considered suitable for all techniques. The variety of heating devices available makes the formulation of one document applicable to all heating methods impossible. We propose that the development of guidelines for each type of hyperthermia method solution, developed by experts respectively in each method, would be more appropriate.

Temperature

When discussing a treatment that involves heat, the logical starting point is the temperature. Early investigations into hyperthermia focused on obtaining temperatures high enough to induce damage within the tumour. It was initially assumed that hyperthermia needed to be in the range of 43 to 45ºC in order to achieve the necrosis of the tumour [71]. Early goals of hyperthermia, therefore, included achieving temperatures of 43ºC and higher. Achieving these temperatures has been problematic. This can be attributed to the variations in physiology, perfusion, and tumour structure at various locations, as well as variations in each patient [74]. The inability to achieve the desired temperature is cited as a major contributing factor to the negative results of the trials listed in Table 1.

A number of positive trials have been published which did not achieve high temperatures. This, combined with research into the effects of moderate heating [75], and review papers such as the one by Dewhirst et al [71] resulted in the broadening of the heating goals of hyperthermia to include a "modest elevation of temperature in the range of 39 to 45°C" [6].

Westermann et al reported a range of average temperatures from 38.6 to 39.7°C in their multicentre study using phased array heating combined with chemoradiotherapy for cervical cancer [58]. The results were positive and led to the development of protocols for a Phase III study which was unfortunately closed early due to poor recruitment [42].

Franckena et al measured an average intraluminal temperature of 40.6°C using a phased array system to heat cervical tumours [16] and Harima et al achieved the same average temperature using capacitive heating, with positive local control results for cervical tumours (although the three year survival rates in the Harima study were not significantly improved) [41]. In a more recent (2019) study by Franckena, T90 measurements from 420 cervical cancer patients treated with a phased array heating system averaged 39.8°C (measured in bladder, vaginal and rectal lumen together and averaged over all treatments per patient) with positive results [76].

Conversely, some studies with sufficiently high temperatures have not shown positive results, such as the multicentre triple therapy study by Harima et al which used capacitive heating and achieved average peri-tumour temperatures of 41.1°C during the treatment of cervical tumours. In this study neither complete response nor five-year survival were improved by the addition of hyperthermia [39]. In a study by Vasanthan et al investigating hyperthermia for the management of cervical cancer, the average intratumoural and intraluminal temperatures was 41.6°C but the local control and three year survival was not significantly improved [38].

In a review by Dewhirst et al., in 2005, the authors discuss the biological effects of hyperthermia at temperatures in the range of 39–42°C and recommend the term "moderate hyperthermia" to describe the heating of tumours to between 39 and 42°C [71]. Subsequent preclinical work confirmed the effects of therapeutic, moderate hyperthermia [77], [78], [79], which is now understood to be below 43°C. Given the variations in resting body temperature of individuals, hyperthermia can further be defined as an elevation in temperature to above the normal body

temperature. As is the case with radiotherapy, the best synergistic action between hyperthermia and chemotherapeutic agents such as cisplatin, carboplatin, and bleomycin appears to occur at temperatures of 41–43°C [2], [10]. Unfortunately, there are also studies which do not show a benefit at moderate temperatures, suggesting that while the temperature may be relevant, it may not be the most important predictor of outcomes.

In an analysis of the relationship between thermal dose (temperature rise and duration of treatment) and clinical outcomes, Kroeson et al defined hyperthermia as a rise in temperature to between 40 and 44ºC. The research group evaluated 204 cervical cancer patients treated with radiotherapy and hyperthermia (phased array) and showed that the thermal dose, along with histology and stage, were significantly associated with local control, survival and disease free survival at three years in single and multivariate analyses. The authors used CEM43T90 and TRISE to measure the thermal dose and although the actual achieved temperatures weren't reported, the median CEM43T90 achieved was 3.51 (IQR 3.09–3.91) and the median TRISE was 3.31 (IQR 1.90–5.54) [80].

Another consideration is vasoconstriction and vasodilation, which are affected by temperature. At temperatures of 38ºC and above, blood flow increases to the tumour which increases oxygen and drug delivery to the tumour. This enhanced perfusion results in improved oxygenation in the target tissue, which enhances the effects of Reactive Oxygen Species induced by ionising radiation [2]. At moderately high temperatures, the healthy tissue can continue to thermo-regulate, but the tumour tissue, as a result of the limited vascular supply, cannot remove the heat as effectively and the tumour continues to heat up faster than the healthy tissue [4]. However vasoconstriction occurs at higher temperatures (>43ºC) and above temperatures of 42ºC the oxygen perfusion declines. Despite the healthy tissue's ability to thermoregulate, prolonged exposure to hyperthermic conditions can still result in tissue damage. The selective heating of the tumours is therefore important in order to minimise damage to the surrounding organs and tissues [5].

Modulated electro-hyperthermia (mEHT) achieves very mild temperature increases. In a study by Lee et al the average peri-tumour temperature measured intravaginally during mEHT treatments to the cervix was 38.5ºC at the end of the treatments with an average increase from the normal body temperature of just under 2ºC [81]. Despite the very mild temperatures achieved, two studies on the cervix have demonstrated improved local control and improved survival using mEHT [14], [82].

Thermometry

The challenge of thermometry in hyperthermia has also limited the wide-spread application of hyperthermia in clinical practices [32]. The insertion of temperature probes has been a standard form of tumoural temperature measurement for many years. Unfortunately, unless the probes are inserted into the tumour, they do not give an accurate picture of the intratumoural temperature. Temperature probes and thermometers are also only able to provide the temperature at a specific point [10], [83]. Recently we have seen an expanding interest in the integration of hyperthermia with MR-guided thermometry.

In order to overcome the variations between patients, it has been recommended that for clinical trials the patient sample be refined to include patients with a tumour of similar size and location and with similar characteristics in order to ensure that the heating conditions between patients are not varied. Strict treatment schedules and the timing of the hyperthermia and radiotherapy/chemotherapy minimise the effect of timing on outcomes and would enable an accurate determination of the relationship between temperature and outcomes [60]. However, in order for this to be accurate, the temperature measurement still needs to be accurate.

This has led to advances in the development of integrated Magnetic Resonance thermometry systems. The advances made in MR-guided thermometry enable researchers to evaluate temperature and potentially perfusion during hyperthermia treatments. These complex MR hybrid hyperthermia systems are available in academic institutes, and the data gathered from collaborations between these institutes are likely to contribute significantly to our understanding of the impact of temperature, timing, and perfusion on the outcomes of hyperthermia treatments [60]. These systems have the potential to contribute to the field significantly; however, they are not practical or feasible for use in clinical settings.

Dose measurement

Proper dose measurement in hyperthermia is essential for the standardisation of the treatments to ensure reproducible results, and to increase acceptance. CEM43 is an abbreviation for cumulative equivalent minutes at a temperature of 43°C, and is the most commonly used method to evaluate the dose in hyperthermia [10]. CEM43, developed in the early 1980s [84], is based on the amount of necrosis that occurs at a temperature

of 43ºC for one hour. Early research showed that heating tumours to 43ºC for 60 minutes or more was associated with a better outcome [85] and some clinical trials have confirmed the positive association between temperature and outcome [46], [60], [85], [86], [87], [80].

According to CEM43, higher temperatures result in more necrosis, and therefore, the treatment time can be reduced. Conversely, lower temperatures should require a longer treatment time in order to achieve the same amount of necrosis. Van Rhoon describes CEM43 as "a normalising method to convert the various time-temperature exposures applied into an equivalent exposure time expressed as minutes at the reference temperature of 43ºC" [60]. Another method of evaluating dose is using the T90, T50, and T10 notations, in which the temperatures are described as those exceeded by 90%, 50%, and 10% of the tumour measurements, respectively. This does not give a picture of the duration of treatments, and intratumoural measurements are not always possible. A combination of these two methods therefore used as a measure of dose: CEM43T90 [2].

While CEM43 has been the standard dosing method for many years and has demonstrated some efficacy in predicting outcomes [71], it is not without limitations. CEM43 is not always associated with the outcomes, as was shown by de Bruijn et al. in a retrospective study in which no clear associations between CEM43ºCT90 thermal dose targets and clinical endpoints were established [88]. CEM43 predicts cell death at a certain temperature, based on the direct cell-killing effects of hyperthermia. There are, however, additional factors in the treatment which contribute to cellular death, other than exclusively the temperature. This is evident by the number of studies with positive results after achieving lower temperatures. Hyperthermia is seldom applied as a monotherapy, and the radio-sensitising and chemo-sensitising effects of hyperthermia, and the resulting cellular damage, are not accounted for in the CEM43 method [60], [71], [89]. The preclinical models on which the CEM43 method is based do not always correlate with the effects in clinical practice, due to the biological variability of humans [89]. For the accurate determination of CEM43, the entire temperature of the tumour must be known, while individual temperature probes only provide temperatures at one location. The homogenous application of heat in traditional heating methods does not guarantee a homogenous temperature in the tumour, which is highly heterogeneous, and it is therefore anticipated that there will be hotter and cooler areas within the tumour. MR-guided thermometry, as discussed earlier, is likely to provide a more effective and accurate real-time measurement of intratumoural temperatures. Unfortunately, the cost and