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Editorial

Dear Readers, Dear Fellow Researchers, Dear Colleagues, Dear Friends,

The recent volume of the Oncothermia Journal is the 28th now. We had started this open-access publication in 2011 intending to provide information for Oncothermia users and interested specialists about the current professional news and results on clinical and experimental topics. I am pleased to recognize the wide interest in the publications and seeing how the Oncothermia Journal started being a reference source for many experts.
The present volume covers many new clinical results. One of the articles presents important data of the abscopal effect of Oncothermia, as well as the low toxicity, which were both proven in a human phase III clinical trial for advanced cervical cancer of HIV positive and HIV negative patients. Important case reports for other cancer types also support the abscopal effect, which is a new stage of oncothermia excellence in advanced, metastatic cases. General research also shows the abscopal effect (this article is in German as it was originally published). The metabolic modifications with ketogenic diet combined with oncothermia had also shown great benefits. Furthermore, a long time awaited clinical study on high dosed vitamin C shows advantages of oncothermia in non-small-cell lung cancer patients as a phase II clinical trial proved, together with the significant improvement of the quality of life of the patients. A review of the clinical pieces of evidence of oncothermia summarizes the important practical results, presenting the clinical successes of the method, following various clinical trials and case reports and achievements of survival time and quality of life of patients. The control of the treatment process during the therapy could be followed by tumor markers, which are also presented in this volume (in German). Important articles deal with the theoretical background of oncothermia. The hypothesis of the effect of modulation, as well as the entropy development of the biological objects, are based on the governing of minimal entropy-production and strengthen the fundaments of the oncothermia method.
I hope this new volume gives you more facilities for your important medical activity and helps your suffering patients.
I am thankful for your attention.

Dr. Andras Szasz
Professor, Chair, Biotechnics Department of St. Istvan University

Liebe Leserinnen und Leser, liebe Kolleginnen und Kollegen aus Forschung und Praxis,

das aktuelle Oncothermia Journal ist mittlerweile der 28. Band dieser Open-Access-Veröffentlichung. Wir haben im Jahr 2011 dieses Projekt ins Leben gerufen, um Oncothermie-Anwendern und interessierten Spezialisten Informationen über Neuigkeiten und aktuelle Ergebnisse zu klinischen und experimentellen Themen zu geben. Ich freue mich über das breite Interesse an der aktuellen Veröffentlichung und die Tatsache, dass das Oncothermia Journal für viele Experten zu einer Referenzquelle geworden ist.
Der vorliegende Band umfasst viele neue klinische Ergebnisse. Einer der Artikel enthält wichtige Daten zum abscopalen Effekt von Oncothermie sowie zur geringen Toxizität. Beides wurde in einer klinischen Phase-III-Studie für fortgeschrittenen Gebärmutterhalskrebs bei HIV-positiven und HIV-negativen Patienten nachgewiesen. Wichtige Fallberichte über andere Krebsarten unterstützen diesen abscopalen Effekt ebenfalls. Dies ist eine neue Etappe für die Oncothermie im Bereich von fortgeschrittenen metastatischen Fällen. Allgemeine Froschungen zeigen den abscopalen Effekt ebenfalls (deutschsprachig). Die metabolischen Veränderungen durch eine Kombination aus einer ketogenen Diät und Oncothermie haben ebenfalls große Vorteile gezeigt. Darüber hinaus belegt eine lang erwartete klinische Phase-II-Studie die signifikante Verbesserung der Lebensqualität durch hochdosiertes Vitamin C in Verbindung mit einer Oncothermiebehandlung bei nichtkleinzelligen Lungenkrebspatienten.
Ein Review der klinischen Evidenzstücke zur Oncothermie fasst die wichtigsten praktischen Ergebnisse zusammen und präsentiert die klinischen Erfolge der Methode, anknüpfend an verschiedene klinische Studien und Fallberichte sowie die Verlängerung der Überlebenszeit und die Verbesserung der Lebensqualität der Patienten. Tumormarker, die ebenfalls in diesem Band vorgestellt werden (deutschsprachige Publikation), können eingesetzt werden um den Behandlungsprozess während der Therapie zu überwachen.
Wichtige Artikel befassen sich mit dem theoretischen Hintergrund der Oncothermie. Die Hypothese des Modulationseffekts sowie die Entropieentwicklung der biologischen Objekte, basierend auf der Beeinflussung der minimalen Entropieproduktion, stärken die Grundlagen der Oncothermie-Methode.
Ich hoffe, dieser neue Band zeigt Ihnen mehr Möglichkeiten für Ihre wichtige medizinische Tätigkeit auf und kann Ihre leidenden Patienten helfen.
Ich bedanke mich für Ihre Aufmerksamkeit

Dr. Andras Szasz
Professor und Vorsitzender der Fakultät für Biotechnik an der St. Istvan Universität

Rules of submission

As the editorial team we are committed to a firm and coherent editorial line and the highest possible printing standards. But it is mainly you, the author, who makes sure that the Oncothermia Journal is an interesting and diversified magazine. We want to thank every one of you who supports us in exchanging professional views and experiences. To help you and to make it easier for both of us, we prepared the following rules and guidelines for abstract submission.

Als redaktionelles Team vertreten wir eine stringente Linie und versuchen, unserer Publikation den höchst möglichen Standard zu verleihen. Es sind aber hauptsächlich Sie als Autor, der dafür Sorge trägt, dass das Oncothermia Journal zu einem interessanten und abwechslungsreichen Magazin wird. Wir möchten allen danken, die uns im Austausch professioneller Betrachtungen und Erfahrungen unterstützen. Um beiden Seiten die Arbeit zu erleichtern, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope

The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to supporting those who would like to publish their results for general use. Additionally, it provides a collection of different publications and results. The Oncothermia Journal is open towards new and different contents but it should particularly contain complete study-papers, case-reports, reviews, hypotheses, opinions and all the informative materials which could be helpful for the international Oncothermia community. Advertisement connected to the topic is also welcome.

- Clinical studies: regional or local or multilocal Oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities and treatment optimization
- Biological studies: mechanisms of Oncothermia, thermal- or non-temperature dependent effects, response to electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- Techniques of Oncothermia: technical development, new technical solutions, proposals
- Hypotheses, suggestions and opinions to improve Oncothermia and electro-cancer-therapy methods, intending the development of the treatments

Further information about the journal, including links to the online sample copies and content pages can be found on the website of the journal: www.oncothermia-journal.com

Umfang und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncothermie-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- Klinische Studien: regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen
- Biologische Studien: Mechanismen der Oncothermie, thermale oder temperaturunabhängige Effekte, Ansprechen auf ein elektrischesFeld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
- Oncothermie-Techniken: technische Entwicklungen, neue technische Lösungen
- Hypothesen undMeinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen

Weitere Informationen zum Journal sowie Links zu Online-Beispielen und Inhaltsbeschreibung sind auf der Website zu finden: www.oncothermia-journal.com

2. Submission of Manuscripts

All submissions should be made online via email: info@oncotherm.org

Manuskripte einreichen

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Texts should be submitted in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be submitted in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be provided in JPG format.

Manuscripts may be any length, but must include:

- Title Page: title of the paper, authors and their affiliations, 1-5 keywords, at least one corresponding author should be listed, email address and full contact information must be provided
- Abstracts: Abstracts should include the purpose, materials, methods, results and conclusions.
- Test: unlimited volume
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- References: Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3]. The full references should be listed numerically in order of appearance and presented following the text of the manuscript.

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Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.
Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.
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- Abstracts: Abstracts müssen Zielsetzung, Material und Methoden, Ergebnisse und Fazit enthalten.
- Text: beliebige Länge
- Abbildungen und Tabellen: Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg eingereicht werden (300 dpi).
- Zitate: Das Oncothermia Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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Bewertung

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Contents

Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients

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www.oncotherm.com/sites/oncotherm/files/2020-06/Minnaar_Abscopaleffect.pdf

Background: A Phase III randomized controlled trial investigating the addition of modulated electro-hyperthermia (mEHT) to chemoradiotherapy for locally advanced cervical cancer patients is being conducted in South Africa (Human Research Ethics Committee approval: M1704133; ClincialTrials.gov ID: NCT03332069). Two hundred and ten participants were randomized and 202 participants were eligible for six month local disease control evaluation. Screening 18F-FDG PET/CT scans were conducted and repeated at six months post-treatment. Significant improvement in local control was reported in the mEHT group and complete metabolic resolution (CMR) of extra-pelvic disease was noted in some participants. We report on an analysis of the participants with CMR of disease inside and outside the radiation field.

Method: Participants were included in this analysis if nodes outside the treatment field (FDG-uptake SUV>2.5) were visualized on pre-treatment scans and if participants were evaluated by 18F-FDG PET/CT scans at six months post-treatment.

Results: One hundred and eight participants (mEHT: HIV-positive n = 25, HIV-negative n = 29; Control Group: HIV-positive n = 26, HIV-negative n = 28) were eligible for analysis. There was a higher CMR of all disease inside and outside the radiation field in the mEHT Group: n = 13 (24.1%) than the control group: n = 3 (5.6%) (Chi squared, Fisher's exact: p = 0.013) with no significant difference in the extra-pelvic response to treatment between the HIV-positive and -negative participants of each group.

Conclusion: The CMR of disease outside the radiation field at six months post-treatment provides evidence of an abscopal effect which was significantly associated with the addition of mEHT to treatment protocols. This finding is important as the combined synergistic use of radiotherapy with mEHT could broaden the scope of radiotherapy to include systemic disease.

Keywords: modulated electro-hyperthermia, abscopal effect, radiotherapy, cervical cancer, immunomodulation

Introduction

The abscopal effect is a systemic response to ionizing radiation (IR) in which non-irradiated lesions respond after irradiation of the primary treatment site (1, 2). It is generally accepted that the abscopal effect is driven by underlying immune mechanisms which are activated by IR (2–4). One proposed mechanism is the immunogenic cell death (ICD) caused by IR (3) which requires the release of damage associated molecular patterns (DAMPs). These in turn activate dendritic cells and enhance antigen expression and presentation to the immune system. Ionizing radiation has also been shown to enhance the functioning of T-cells (4).

The frequency of reported abscopal effects in the literature is extremely low with only a handful of published cases per year (3, 4). In a review, Reynders et al. summarized 23 case reports, one retrospective study, and 13 pre-clinical papers, from the 1970s to 2014. Only one of these involved a primary squamous cell carcinoma of the cervix. The patient (age 69 years) was treated with external beam radiation (EBRT) and brachytherapy (BT) for locally advanced cervical cancer (LACC) and showed a complete response of the para-aortic nodes outside of the radiation field, as well as a complete response of the tumor, on the post-treatment Abdominal and Pelvic Computed Tomography (CT) and Pelvic Magnetic Resonance Imaging (MRI) scans (5). Reynders et al. concluded that the abscopal effect is based on anti-tumor immunity and was more common in immunogenic tumor types. Renal cell carcinoma had the most frequently reported cases of the abscopal effect followed by hepatocellular carcinoma. The abscopal effect was observed at all ages and with a variety of radiotherapy protocols. The preclinical data indicates that some immunomodulatory agents may have potential to act synergistically with IR to induce a systemic response (4) which may

explain the increase in the number of reported abscopal effects with the combined treatment of immunotherapies and IR (6).
The addition of mild hyperthermia to local irradiation has shown to have immunomodulating effects which may result in enhanced tumor regression and an abscopal effect when combined with radiotherapy, as was seen in a liposarcoma patient treated with hyperthermia and radiotherapy (7). Hyperthermia may directly activate the immune cells present in the tumor and its microenvironment (8) and may further enhance the function of the dendritic cells (9).

Modulated electro-hyperthermia (mEHT) applies amplitude modulated radiofrequency (13.56 MHz), in a capacitive coupling set-up to target and heat malignant tissues, sensitizing them to treatments. The technique exploits the differences in impedance between the malignant and healthy tissue as well as impedance matching technology, to selectively deliver an energy to the malignant tissues. The energy deposition has the net effect of an increase in the thermal energy, and temperature. The biophysics are further described in detail in the literature (10–12). Preclinical research suggests that mEHT combined with immunotherapies is able to elicit an immune-mediated response (13) which may even extend to untreated tumors. Vancsik et al. showed that mEHT induced DAMPs in murine models was followed by an invasion of antigen presenting cells (APC) and T-cells at the site of the treated tumor and that when mEHT was administered combined with a T-cell stimulating agent, APC and T-cell invasion was also seen in the untreated tumors of the same murine model (14). In an in vivo study, mEHT combined with dendritic cell therapy elicited a response to untreated tumors in murine squamous cell carcinoma (SCCVII) models (15). Ionizing radiation has shown to increase the expression of immunogenic molecules such as calreticulin, on the surface of tumor cells and radiation-induced stress-response leads to the expression of heat shock protein70 (HSP70) on cell membranes. This Heat Shock Protein plays an important role in mounting an immune response at the site when released into the extracellular matrix (16). Yang et al. reported an increased release of the expressed HSP70 and increased levels of calreticulin after mEHT, compared to other heating methods (17).

The safety and heating efficacy of mEHT in cervical cancer patients has been demonstrated (18–20). Minnaar et al. (19) reported on local disease control in an ongoing randomized controlled trial investigating the effects of the addition of mEHT to chemoradiotherapy (CRT) protocols for the treatment of LACC. The trial was conducted in a resource-constrained setting and in high risk patients in South Africa. In the report, 202 participants were eligible for six month local disease-free survival (LDFS) and local disease control (LDC) (mEHT: n = 101; Control: n = 101), of which 171 [mEHT: n = 88 (87.1%); Control: n = 83 (82.2%)], were alive at six months post-treatment. Participants in the mEHT group had a higher LDC and complete metabolic response of the tumor (45% and 58%), than those in the Control Group (24% and 36%), (p = 0.005 and p = 0.003, respectively), and were significantly more likely to achieve six month LDFS (OR: 0.36, 95% CI: 0.19-0.69; p = 0.002) (19). During the LDC analysis, it was noted that some of the participants with extra-pelvic disease present on the pre-treatment Fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) /CT scans showed a complete metabolic resolution (CMR) of disease outside the treatment field on the post-treatment 18F-FDG PET/CT scans. An analysis of the subset of patients with extra-pelvic disease visualized on the pre-treatment 18F-FDG PET/CT scans was subsequently planned. We present the results of this analysis with the aim of investigating the possibility of an abscopal effect induced by the addition of mEHT to CRT in these participants.

Methods and Materials

A Randomized controlled trial by Minnaar et al. (19) is being conducted at the Charlotte Maxeke Johannesburg Academic Hospital, a public hospital in Johannesburg, South Africa, by the Radiation Sciences department of the University of the Witwatersrand. The trial was registered on the South African National Clinical Trials Register before recruitment was started (ID:3012) and approval from the Human Research Ethics Committee was obtained (M704133/M190295). The trial was registered at ClincialTrials.gov (NCT03332069). Enrolment began in January 2014 and was closed in November 2017.

Two hundred and ten participants were randomized to receive either CRT alone (Control Group) or combined with mEHT (mEHT Group). Randomization was conducted using the REDCap on-line computer generated random-sampling tool with stratification according to HIV status and accounting for age and FIGO stage. Physicians reporting on the 18F-FDG PET/CT scans were blinded to treatment allocation and did not interact with the participants, eliminating the risk of biased reporting.

Eligibility

Eligibility criteria for the trial: Females with International Federation of Gynecology and Obstetrics (FIGO) (21) stages IIB to IIIB primary, treatment naïve, histologically confirmed squamous cell carcinoma of the cervix (staged based on clinical examination, chest radiography, and a pelvic ultrasound) eligible for CRT with radical intent; Signed informed consent; >18 years old; Eastern Cooperative Oncology Group (ECOG) score <2; Creatinine clearance >60 mL/min. Screening evaluations included full blood count, urea and creatinine levels, liver function, Human Immunodeficiency Virus (HIV) test; and a CD4 count if necessary. An 18F-FDG PET/CT scan was performed on eligible participants prior to commencement of therapy, as a baseline study against which response to treatment could be measured. Participants with bilateral hydronephrosis, visceral metastases, or fistulas visualized on the 18F-FDG PET/CT scan were excluded from the study. HIV-positive patients were included provided their CD4 count was above 200 cells/μL and/or they had been on antiretroviral therapy (ART) for more than six months.

Exclusion Criteria for the trial: Bilateral hydronephrosis; Second primary malignancy/prior malignancy treated in the preceding two years; vesicovaginal fistula or rectovaginal fistula that required a change in treatment protocols; Abnormal liver function tests; Pregnant or breast feeding; Prior hysterectomy; Cardiovascular disease (excluding controlled hypertension); Acute or life-threatening infections or medical conditions; Contraindications to any of the prescribed treatments.

At the time of this analysis all participants were a minimum of six months post-treatment and local disease control data at six months post-treatment was available for all participants (19). Participants were considered eligible for the sub-analysis presented in this report if: They met all the trial eligibility criteria; the pre-treatment 18F-FDG PET/CT scan showed FDG-avid (SUV > 2.5) nodal disease outside of the pelvic treatment field; and the participants had a post-treatment 18F-FDG PET/CT scan.

Data Management

Participant data was captured using REDCap (Research Electronic Data Capture), an online, secure web-based application hosted by the University of the Witwatersrand.

Treatment

All participants were planned to receive 50Gy in 25 fractions EBRT to the whole pelvis and 24Gy in 3 fractions of high dose rate (HDR) BT (36Gy equivalent dose in 2Gy fractions for an alpha-beta ratio of 10; source used: Iridium-192) and two doses of cisplatin (80 mg/m2) administered 21 days apart (subject to the participant's fitness to receive cisplatin), as per institutional protocol. The goal of RT was for participants to receive a total dose of 86Gy equivalent by the combination of EBRT and BT. External beam radiation to the whole pelvis was delivered using a two dimensional four-field-box technique to include the tumor and pelvic nodes. Participants were simulated supine. The superior border of the Anterior-Posterior and Posterior-Anterior (AP-PA) field was mid-L5. The inferior border was either the inferior part of the ischial tuberosity or the lowest extension of the tumor with at least a 2 cm margin, whichever was lower. The lateral borders were 2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the superior and inferior borders were the same as for the AP-PA fields. The anterior border was the mid to anterior third of the symphysis pubis and the posterior border was S2–S3 to include the presacral nodes and possible tumor extension along the uterosacral ligament.

Modulate electro-hyperthermia (Model: EHY2000+; Manufacturer: Oncotherm GmbH, Troisdorf, Germany) was administered twice per week (maximum ten treatments), at a maximum power of 130 W, immediately before EBRT (maximum 30 min from completion of mEHT to completion of EBRT). Step-up heating protocols were adhered to and mEHT treatments were administered at least 48 h apart. A 30 cm diameter round electrode was used and treatment duration was 55 min at the final power output, with a minimum planned energy dose of 360 KJs. Details of the technique are described elsewhere in the literature (11, 19, 22).

Outcome Measures

Nodes with FDG-avid disease were grouped by region on the pre-treatment scans: Head and Neck; Thorax; Abdomen (including the upper pelvis outside of the radiation field); and Pelvis (within the radiation field). The standard uptake value (SUV) cut-off was considered to be 2.5 and evaluation of the 18F-FDG PET/CT scans was based on PERSIST 1.0 Criteria. Tumor response was classified as Complete Metabolic Response (CMR); Partial Metabolic Response (PMR); Stable Metabolic Disease (SMD); Progressive Metabolic Disease (PMD) (23). On the follow-up scans each region was scored as: no change; resolved nodes; new nodes. Only the complete metabolic response of all disease (nodes outside of the radiation field, nodes inside the radiation field, and the tumor), as visualized on post-treatment 18F-FDG PET/CT scans, was considered an indicator of the abscopal effect.

Statistics

The frequency of the observed abscopal effect was compared by group (mEHT or Control) and HIV status (positive or negative) using a Chi-squared frequency table. Paired t-test was used to compare the difference in means between groups and logistic regression was used to test prognostic factors. Two-sided p values are reported and $p < 0.05$ were considered significant. STATA 13.0 Statistics software program (Stata Corporation, College Station, Texas, USA), was used to analyze the data.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (M120477 and M190295) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Characteristics

Two hundred and ten participants were randomized for treatment, of which 146 (70%) had FDG-avid nodal disease visualized outside of the radiation field on the pre-treatment 18F-FDG PET/CT scans (mEHT Group: n = 68 (64%); Control Group: n = 78 (75%)). One hundred and eight of the participants with extra pelvic nodal disease survived six months post-treatment and were eligible for the post-treatment 18F-FDG PET/CT scans (mEHT Group: n = 54 (79%); Control Group: n = 54 (69%)) and were therefore included in this analysis. The characteristics, including treatment characteristics, of these 108 participants are listed in Table 1. The number of participants (grouped by treatment group and HIV status) with nodes visualized in each region on the pre-treatment 18F-FDG PET/CT scans are shown Figure 1. The median number of weeks between the final RT treatment and the follow-up 18F-FDG PET/CT scans was 26.3 in the mEHT Group (Q1: 25.3; Q3: 27.3) and 27 in the Control Group (Q1: 26; Q3: 29).

		mEHT 54	Control 54	
FIGO Staging	IIB	25 [46%]	22 [41%]	
	III	29 [54%]	32 [59%]	
Race	African	51 [94%]	52 [96%]	
	Caucasian	1 [2%]	0 [0%]	
	Other	2 [4%]	2 [4%]	
Age [years]	Mean	49.3	49.9	$p = 0.776$
	SD	9.98	9.99	
	Range	30–68	28–70	
BMI	Mean	28.7	27.0	$p = 0.127$
	SD	5.61	6.01	
	Range	18–44	15–39	
Total RT dose (EQD2)	Mean	85.7Gy	86Gy	$p = 0.251$
	SD	1.65	0	
	Range	74–86Gy	86Gy	
No of Cisplatin doses	Mean	1.37	1.25	$p = 0.321$
	SD	0.69	0.76	
	0 doses	5 [9%]	6 [11%]	
	1 dose	19 [35%]	20 [37%]	
	2 doses	30 [56%]	28 [52%]	
Days between final RT and PET/CT	Mean	188.2	193.4	$p = 0.242$
	SD	24.05	22.15	
	Range	54–310	155–266	
CD4 count [cells/μL]	Mean	552.9	543.9	$p = 0.089$
	SD	264.15	276.36	
	Range	194–1077	134–1524	
No of mEHT doses	Mean	9.54		
	SD	1.07		
	Range	4–10		
Average KJ administered during mEHT	Mean	382.6 KJ		
	SD	29.95		
	Range	259–427 KJ		

No significant differences in characteristics and treatment were seen between the two groups. mEHT, Modulated Electro-Hyperthermia; FIGO, Federation of Gynecology and Obstetrics; SD, Standard Deviation; BMI, Body Mass Index; RT, Radiation Therapy; PET/CT, Positron Emission Tomography / Computed Tomography; KJ, Kilojoules.

Table 1. Characteristics of participants eligible for analysis of the abscopal effect.

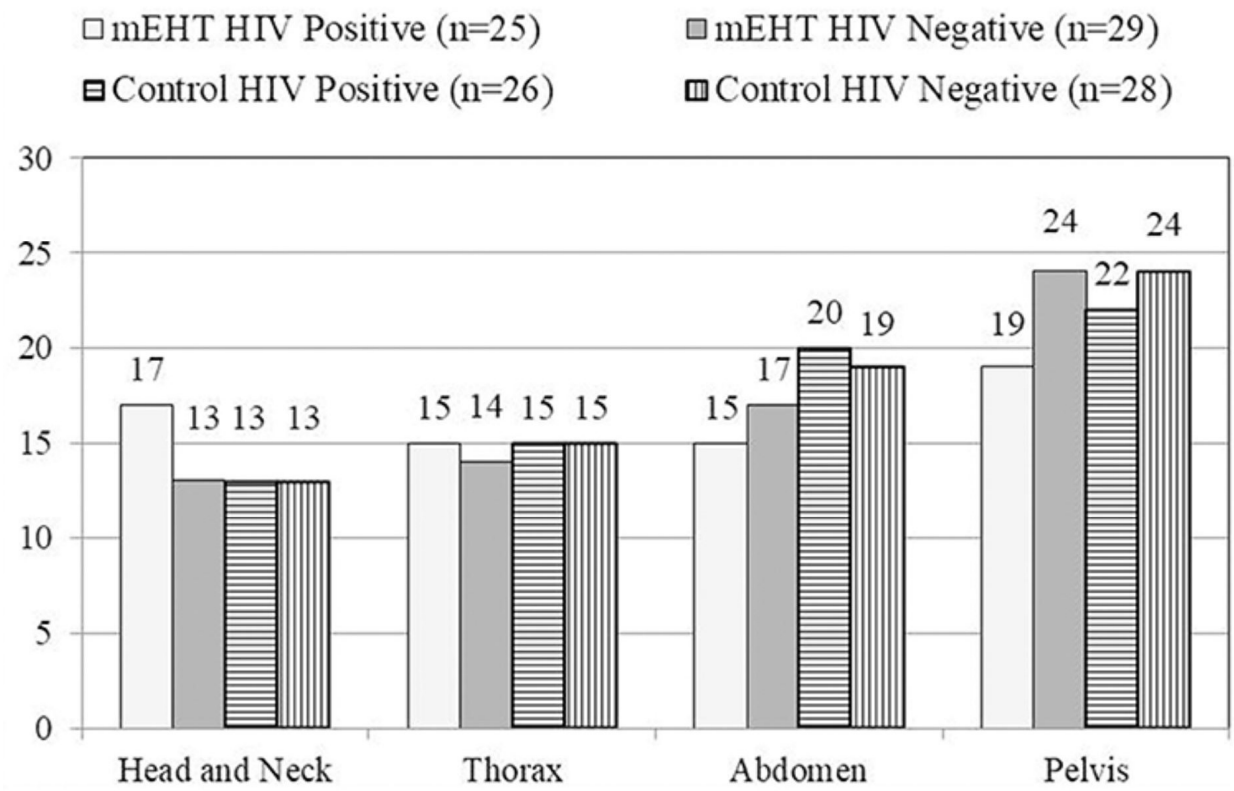

Figure 1. Number of patients with nodes visualized by region. The number of participants with nodes visualized in each region is represented graphically, showing a similar pattern in all participants in each treatment group on the pretreatment 18F-FDG PET/CT. mEHT, Modulated Electro-Hyperthermia; HIV, Human Immunodeficiency Virus.

Abscopal Effect as Visualized on 18F-FDG PET/CT

An abscopal response was only considered if all disease, including the primary tumor, nodes within the radiation field, and all nodes outside of the radiation field showed a complete metabolic response (SUV <2.5) on the six month post-treatment 18F-FDG PET/CT. Therefore all participants who had an abscopal effect also showed local disease control (a complete metabolic response of the tumor and nodes within the pelvic radiation field). The percentage of participants with complete resolution of all metabolically active disease on six month post-treatment 18F-FDG PET/CT scans was higher in the mEHT group: n = 13 (24.1%) than in the control group: n = 3 (5.6%) (Chi-squared: p = 0.013). There was no significant difference in the response between the HIV-positive (n = 51) and -negative (n = 57) groups (HIV-positive: n = 7 (13%); HIV-negative: n = 9 (16%); Chi-squared: p = 0.793) with a close to even split in frequency of abscopal responses observed between the HIV-positive and -negative participants in each treatment group, as seen in Figure 2. In a multivariate analysis (confidence interval (CI) 95%) of age, cisplatin cycles, total radiation dose, and the number of days between the final radiation treatment and the follow-up 18F-FDG PET/CT, none of the variables were indicators of an abscopal effect (Age: OR:1.01, p = 0.692, CI: 0.96-1.07; Cisplatin cycles: OR: 1.20; p = 0.671; CI: 0.51-2.83; Days to PET/CT: OR: 1.01; p = 0.283; CI: 0.99-1.07; Total RT: OR: 0.66; p = 0.316; CI: 0.30-1.47). In a univariate analysis, the CD4 count of participants was also not predictive of an abscopal effect (OR: 1.00, p = 0.893, CI: 0.997–1.003). In the participants in whom an abscopal effect was observed, the mean time between the final radiation and the follow-up 18F-FDG PET/CT was 196 days (range 162–266).

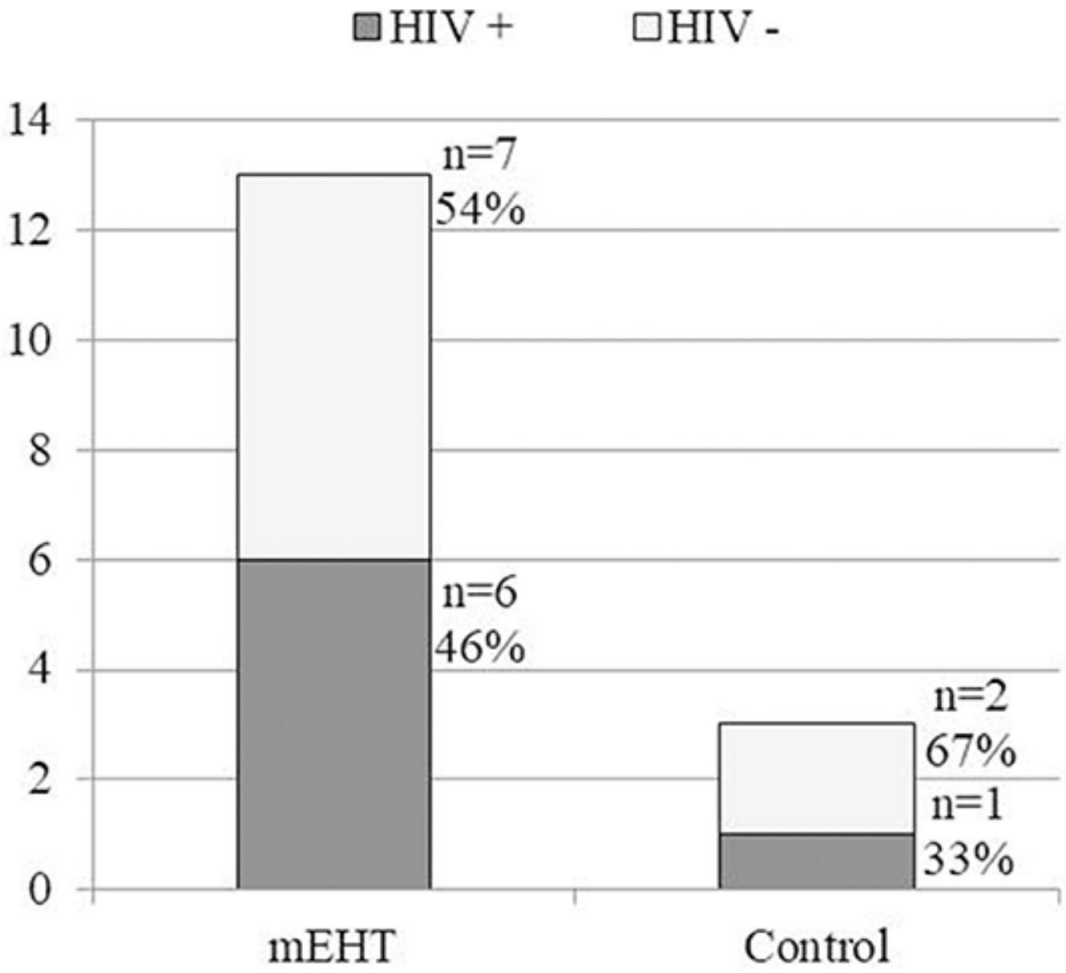

Figure 2. Frequency of observed abscopal effect in HIV-positive and HIV-negative participants in each treatment group. A significant difference between the frequency of abscopal effect was noted between the mEHT Group (13 out of 54(24.1%)) and the Control Group (3 out of 54 (5.6%)) (p = 0.013). There was no significant difference in frequency of the observed abscopal between the HIV-positive and HIV-negative participants. mEHT, Modulated Electro-Hyperthermia; HIV, Human Immunodeficiency Virus.

Follow up

One participant had visceral disease on the pre-treatment 18F-FDG PET/CT scan: multiple lung nodules (highest SUV in the left lung of 6.03 and the right lung of 4.38) and a lesion in the T11 vertebra (SUV 9.71). This participant was in the mEHT group. The follow-up 18F-FDG PET/CT scan showed no sign of metabolically active disease. This participant is 18 months post-treatment and is still disease free. Of the participants who showed an abscopal effect, seven out of 13 mEHT participants and two out of three control participants have reached 2 years post treatment and are still disease free. Two participants in the mEHT group and one in the Control group demised before reaching two years (cause of death: acute renal failure). Four participants in the mEHT group have not yet reached two years post treatment (two are 18 months and two are 12 months post-treatment), however they are still disease free. Table 2 lists all the sites of FDG avid disease seen in the participants in whom an abscopal response was observed, the disease-free survival observed, the viral load, CD4 count, and the HIV status of the participants.

HIV status	Days to PET	No. ChT	Description of extra-pelvic disease on pre-treatment PET/CT	Survival
mEHT group				
Pos. (CD4: 863; VL:27)	211	2	Common carotid (SUV 7.5); Para tracheal (SUV 4.41); Axillary (SUV 5.59)	2YDFS
Pos. (CD4:194; VL:<20)	163	1	Bilat. Jugular. digastric (SUV Left: 2.62; Right: 3.34); Axillary (SUV 4.49); Pre- (SUV 2.75) and Sub-carinal (SUV 3.16); Retrocrural (SUV 3.47) Bilat. PA (SUV Left: 2.59; Right: 3.39)	OS: 335
Pos. (CD4: 905; VL:<20)	200	2	Jug. Digastric (SUV 2.6); Hilar (SUV 2.92)	2YDFS
Pos. (CD4: 845; VL: ND)	190	2	Bilateral supraclav. (SUV Right: 6.04; Left: 2.94)	2YDFS
Pos. (CD4: 456; VL: ND)	192	2	7 Bilat. cervical (highest SUV4.81); Axillary (SUV 4.24); Subcarinal (SUV 2.73); CI (SUV Right: 2.93; Left: 4.73)	2YDFS
Pos. (CD4: 284; VL:196)	182	2	Bilat. Jug. Digastric (SUV Right: 7.42; Left: 2.72); CI (SUV 3.89)	DF at 18 m
Neg.	185	1	Aorto-pulmonary (SUV 2.75)	2YDFS
Neg.	197	1	PA (SUV 4.73)	2YDFS
Neg.	185	2	Cervical (Level IIA SUV 5.67; Level IIB SUV 3.49)	2YDFS
Neg.	183	0	Bilat. axillary (SUV Left: 2.87; Right 2.98)	OS: 596
Neg.	193	2	Supraclav. (SUV 7.42); Paratracheal (SUV 20.38); Aorto-pulmonary (SUV 14.72); Bilat. hilar / Peribronchial (SUV Right 17.86, Left 13.47); Multiple Pulmonary nodules (SUV Right 6.03, Left 4.38); T11 (SUV 9.71)	DF at 18 m
Neg.	224	1	Coelic axis (SUV 7.93)	DF at 12 m
Neg.	189	2	Aorto-pulmonary (SUV 4.1); Pre-carinal (SUV 3.7)	DF at 12 m
Control				
Pos. (CD4: 564; VL: ND)	207	0	PA (SUV 3.35); CI (SUV 4.5 0.9)	OS: 483
Neg,	266	2	Aorto-pulmonary (SUV 2.79); PA (SUV 4.21)	2YDFS
Neg.	183	2	PA (SUV 4.81); Paravertebral (SUV 6.56)	2YDFS

**An abscopal response was considered if there was complete metabolic resolution of the extra-pelvic disease and pelvic disease, including the tumor and pelvic nodes, on the post-treatment ^{18}F-FDG PET/CT scans, with an SUV of <2.5. ChT, Chemotherapy; CI, Common Iliac; DF, Disease Free; HIV, Human Immunodeficiency Virus; mEHT, Modulated Electro-Hyperthermia; ND, Not Detectable; OS, Overall Survival; PA, Para aortic; SUV, Standard Uptake Value; YDFS, Years of Disease Free Survival; VL, Viral Load.*

*Table 2. Details of the extra-pelvic disease in participants with an *Abscopal Effect.*

HIV Status

In order to rule out the effects of HIV on the visualization of nodes, the cases were reviewed with the intention of discarding cases which had nodes known to be visualized in HIV disease. HIV-positive participants with high viral load levels may have benign hypermetabolic foci visualized on 18F-FDG PET/CT images, resulting in false positive interpretations of malignancy (24). Furthermore, Sathekge et al. showed that the CD4 count of HIV positive participants was inversely proportional to the FDG uptake in the nodes (25). During acute HIV infection FDG uptake increases in the head and neck lymph nodes, in mid stage of HIV infection hypermetabolism occurs in cervical, axillary, and inguinal lymph nodes, and an increased FDG uptake occurs in the colon, mesenteric, and ileocecal lymph nodes during late HIV disease (24). None of our participants were in acute (newly diagnosed) or late stage (no Acquired Immune Deficiency Syndrome-defining illnesses other than cervical carcinoma) of HIV infection. Four of the participants with an abscopal response showed increased FDG uptake in the axillary glands: one was HIV-negative and was therefore still included, three were HIV-positive and all had increased FDG uptake in extra-pelvic nodes other than the axillary nodes. These three

participants were therefore still included. Of the seven HIV-positive participants, one had increased FDG uptake in the inguinal nodes however several other extra-pelvic nodes were also visualized and the patient was included.

Discussion

The CMR of disease outside the radiation field at six months post-treatment in our sample provides evidence of an abscopal effect. The frequency of the observed abscopal effect was significantly associated with the addition of mEHT. This finding is important as methods to enhance the abscopal effect could broaden the scope of ionizing radiation from a local treatment to a systemic and potentially curative modality for metastatic and systemic disease. The abscopal effect was seen equally in HIV-positive and -negative participants in the group treated with mEHT. This suggests that the potentiation of the systemic, immune-mediated response to IR was not inhibited by HIV-infection and could still be possible in such high-risk patients.

Reynders et al. reported that the median time to achieve an abscopal response was five months, ranging from 1 to 24 months (4). In our study we assessed the abscopal effect as part of the disease response at six months, which corresponds to the findings by Reynders et al. In their review Reynders et al. report on patients who had received multiple fractions of radiotherapy followed by a reduction in size/metabolic activity of a non-irradiated lesion (partial response). In our report we present only participants who showed a complete metabolic response of all disease, including the primary tumor. This strengthens the probability of an abscopal response in our participants. Reynders et al. excluded papers in which systemic cytotoxic drugs were administered (4). We have included participants who were treated with cisplatin as a radiosensitiser, however the administration of cisplatin to participants in the mEHT Group and Control group was evenly matched suggesting that the difference between responses in the two groups was not the due to the cisplatin and is associated with the addition of mEHT. Furthermore, cisplatin was not a predictor of an abscopal effect in our sample.

The rarity of the abscopal effect documented in the literature suggests that the abscopal effect alone is unlikely to impact clinical regimes and influence treatment choices (3). Considering their immune components, the combination of radiotherapy with immunotherapies and mEHT may provide an opportunity to boost abscopal response rates. Reynders et al. reported on four case reports of the abscopal effect using Ipilimumab (one in adenocarcinoma of the lung and three in melanoma patients), one using BCG-vaccination (adenocarcinoma of the lung) combined with IR, and one retrospective study in which 11 out of 21 melanoma patients treated with Ipilimumab followed by palliative radiotherapy showed an abscopal response (4). The increase in use of immunotherapies combined with IR has resulted in an increase in the reports of abscopal effects. At least ten trials have been registered on ClincialTrials.gov to investigate the effects, including the abscopal effect, of immunotherapies combined with IR. The lack of reliable biomarkers to predict and confirm the presence of an abscopal effect may impact on the future optimization of protocols to induce an abscopal effect. An important future field of investigation is therefore the development of biomarkers which can reliably predict and quantify the presence of an abscopal effect.

Preclinical data on the synergistic effects of immunomodulating agents and mEHT with IR, as well as case reports, and the results of this study, provide strong support for the development of trials on the combined use of IR with mEHT and immunotherapies. Positive results in such trials would broaden the scope of ionizing radiation from local or palliative treatment to a potentially curative modality in metastatic and systemic disease.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Human Research Ethics Committee approval number: M120477) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.20

Author Contributions

CM: conducted the research, gathered the data, statistical analysis, interpretation of results, and writing of the manuscript. JK: planning and prescribing of treatments, oversaw the treatment and follow-ups of trial participants, and reviewed manuscript. OA: reviewed 18F-FDG PET/CT reports, reviewed manuscript. M-D-TV: oversaw all the 18F-FDG PET/CT scans and related logistics, reviewed manuscript. AB: supervised data collection and data quality control, project planning, management of funding, and reviewed manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Keywords: modulated electro-hyperthermia, abscopal effect, radiotherapy, cervical cancer, immunomodulation

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Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients

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Abstract

Introduction: HIV infection is associated with increased treatment-related toxicity and worse outcomes in locally advanced cervical cancer patients (LACC), especially in resource-constrained settings. Local control (LC) in a phase III randomized, controlled trial investigating modulated electro-hyperthermia (mEHT) on LACC patients in South Africa (ethics registration: M120477/M190295), was significantly higher in participants randomized to receive chemoradiotherapy (CRT) with mEHT compared to CRT alone (stratum: HIV status, accounting for age and stage). This analysis investigates whether mEHT adds to the toxicity profile of CRT in HIV-positive LACC participants.

Methods: Inclusion criteria: signed informed consent; International Federation of Gynecology and Obstetrics stages IIB to IIIB squamous cell carcinoma of the cervix; HIV-positive patients: CD4 count >200 cell/µL/on antiretroviral treatment for >6 months; eligible for CRT with radical intent. Recruitment: January 2014 to November 2017 (ClinicalTrials.gov: NCT03332069). Acute toxicity (evaluated using CTCAE v4 criteria) and quality of life (according to EORTC forms) in 206 participants randomized for treatment were evaluated alongside the LC results to determine safety and efficacy in HIV-positive participants.

Results: Compliance to mEHT treatment was high (97% completed ≥8 treatments) with no significant differences in CRT-related toxicity between treatment groups or between HIV-positive and -negative participants. Adverse events attributed to mEHT were minor, even in obese patients, and did not affect CRT compliance. Participants treated with mEHT reported improved fatigue, pain, emotional and cognitive functioning.

Conclusion: mEHT did not cause unexpected CRT-related toxicities and is a safe treatment modality for HIV-positive patients, with minor limitations regarding body weight, even in a low-resource setting.

Keywords: Modulated electro-hyperthermia, chemoradiotherapy, cervical cancer, early toxicity, quality of life, HIV

Introduction

The incidence of locally advanced cervical cancer (LACC) in developed countries has decreased since the introduction of screening and Human Papilloma Virus (HPV) vaccination programs [1,2], yet morbidity and mortality rates remain high in low-resource settings [3]. Radiotherapy (RT) with weekly concurrent cisplatin is the standard of care for LACC [4], however in patients who are unable to receive cisplatin, hyperthermia (HT) delivered at 40–43 °C for 60–90 min has shown to be as effective as a radiosensitizer [5]. Studies have shown that HT plus RT improves local disease control (LDC) and survival in LACC patients, compared to RT alone, without significant effects on RT-related toxicity [6–10]. Hyperthermia has been investigated as a chemo-sensitizer with response rates of more than 50% and acceptable toxicity for the management of recurrent or residual cervical tumors [11,12] and phase II studies have demonstrated the safety of the addition of HT to chemoradiotherapy (CRT) [13–15]. Adverse events directly attributed to HT include pain (8%), superficial burns (6–18%) [10,13], subcutaneous fatty burns (8–12%) [5,10,11,13], and infections after the introduction of interstitial thermometry catheters [10]. A retrospective analysis of 420 patients treated with RT and HT reported that 153(36%) participants developed subcutaneous tissue toxicity, ranging from grade 1–3 in severity, with one patient requiring surgical intervention [16]. Acute neurotoxicity following the treatment of deep pelvic tumors with HT is a rare (2.3% incidence) complication which can have an impact on the daily activities of the patient [5,17].

The effect of HIV infection on the treatment of LACC patients includes increased multi-system RT-related toxicity, treatment interruptions, higher risks of residual disease [18] and lower survival rates [19]. Increased chromosomal radio sensitivity has been observed in the lymphocytes of HIV-positive

patients, compared to HIV-negative patients [20,21]. Fibroblasts from the skin of HIV-positive Kaposi Sarcoma patients are more sensitive to ionizing radiation (IR) when compared to those of healthy controls [22] and extreme mucositis has been reported in HIV-positive patients [23]. Housri et al. [24] recommend that HIV-positive patients treated to the head and neck, abdomen and pelvis, with RT, should be closely monitored for possible mucosal reactions and HIV-positive patients treated with CRT should be closely monitored for hematologic toxicity. Possible contributors to the increased radio sensitivity of HIV-positive patients include a systemic glutathione deficiency caused by HIV infection, resulting in the depletion of radio-protective thiols and increased oxidative stress [25], and the effect of the HIV-1 Tat protein on the cellular capacity of certain cells to repair radiation-induced DNA double strand breaks [24]. Information on the use of modulated electro-hyperthermia (mEHT) as a radiosensitizer in HIV-positive patients, who may be more likely to experience RT-related toxicity, is not available and therefore requires investigation.

mEHT

mEHT is a capacitive technology which transmits amplitude modulated radiofrequency (RF) waves at a frequency of 13.56 MHz, between two electrodes [26–29]. The small electrode is covered by a water bolus in an adjustable arm, and the large electrode is in the bed and is covered by a water mattress. The amplitude modulation, which is the main difference between mEHT and other capacitive devices, is described elsewhere in the literature and is purported to be a key component of the enhanced efficiency of mEHT, allowing for a lower power output [29,30]. The effects of the amplitude modulation are not yet fully understood and are still under debate.

Preclinical studies have shown that mEHT is distinctly more effective than water-bath, infrared, or RF-hyperthermia, if adjusted to the same temperature [31] and mEHT, when applied at 42 °C, induces both thermal and non-thermal effects on cells. In a study by Andocs et al. [32], the ratio of cell killing was enhanced by a factor of 3.2 in tumors treated with mEHT at 42 °C in comparison to tumors treated with infrared heating at 42 °C, reflecting the non-thermal effects of mEHT and the potentiation of the effects of radiofrequency heating at 13.56 MHz by the addition of amplitude modulation.

Lee et al. [33] observed an increase in temperature to a maximum average of 38.5 °C in cervical tumors after 60 min heating at a planned power output 150 W (although the actual power output is not described in the article), which is 20 W higher than our planned maximum power output. This was accompanied by an increase in blood perfusion. The same group showed that mEHT combined with platinum-based chemotherapy improved outcomes for recurrent/residual disease in cervical cancer patients [34]. The mild temperatures reached during mEHT treatments alone cannot explain the improved outcomes seen after the mEHT treatments, confirming the importance of the addition of amplitude-modulation. The specific interaction of mEHT in tumors allows for an effective treatment with less total power in comparison to conventional RF-systems. The data reported in the studies by Lee et al. [33,34] provided the rationale to evaluate the use of mEHT for the primary management of locally advanced and nonresectable cervical cancer.

mEHT is being investigated in a phase III randomized controlled trial as a radiosensitizer (whole pelvic radiation), combined with cisplatin, for the treatment of LACC in a low-resource setting and in HIV-positive and -negative patients. This is the first randomized controlled trial on mEHT combined with CRT for LACC, and the only study in a low-resource setting and in HIV-positive patients. Table 1 summarizes the local control (LC) outcomes at six months post-treatment, as reported by Minnaar et al. [35]. Two hundred and two participants were eligible for LC analysis (mEHT: n = 101; Control: n = 101) at 6 months post-treatment, of which 171 (mEHT: n = 88 (87.1%); Control: n = 83 (82.2%)), were alive at six months post-treatment. The study did not show any significant difference in treatment related toxicity between the two treatment groups [35].

Table 1. Summary of local control outcomes at 6 months post-treatment in the trial by Minnaar et al. [35].

	mEHT group	Control group	*p*-value
Tumor response on PET/CT	49/85 (58%)	26/73 (36%)	0.005
LC censored for survival	40/88 (45%)	20/83 (24%)	0.003
LDFS	39/101 (39%)	20/101 (20%)	0.003

PET/CT: position emission tomography/computed tomography; LC: local control; LDFS: local disease free survival.

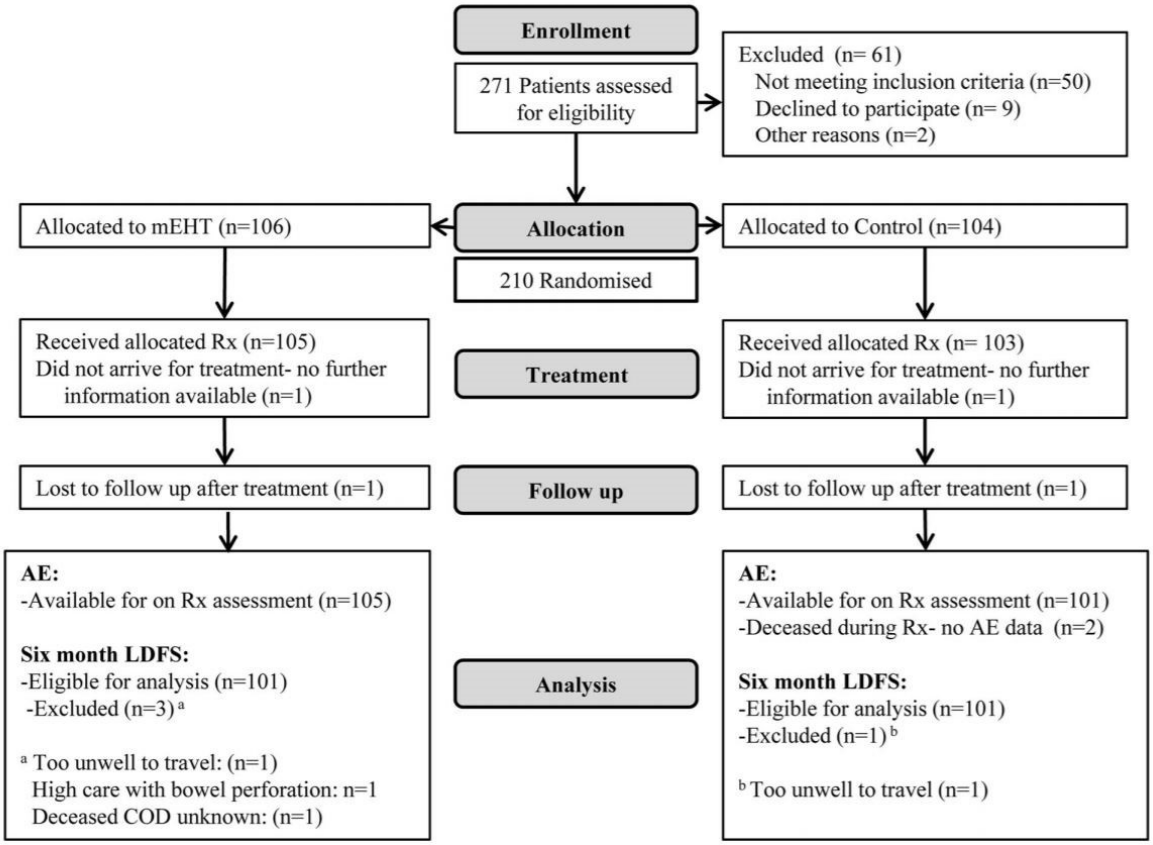

Figure 1. CONSORT diagram of the 271 patients who were screened and subsequently included or excluded in the trial, as reported by Minnaar et al. [35] and available for evaluation of early toxicity. AE: adverse events; COD: cause of death; LDFS: local disease free survival; Rx: treatment.

Participants who were eligible for evaluation of LC by 18Fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) scans (creatinine clearance >60 ml/min, controlled glucose levels, were able to lie still for the duration of the scan), had a second 18F-FDG PET/CT scan at six months post-treatment. Local control was considered a failure if any disease was confirmed either by 18F-FDG PET/CT, CT, clinical examination, cytological evaluation or fine needle aspiration of palpable lymph nodes in the radiation field. Participants treated with mEHT were significantly more likely to achieve six-month local disease-free survival (LDFS; odd ratio (OR): 0.36, 95% confidence interval (CI): 0.19–0.69; p = 0.002) and the association between HIV status and six month LDFS was not significant (p = 0.338). The authors reported that the age, number of cisplatin doses, treatment time, RT dose, and CD4 count, were not significant predictors of six-month LDFS. In the mEHT group, body mass index (BMI), number of mEHT treatments, and energy dose were not predictors of six-month LDFS. In a preliminary report on the first 70 participants in the study to reach two years post-treatment, two year survival was more likely in the participants treated with mEHT

(78 vs. 65%; Prob> $\chi 2 = 0.0334$; adjusted for age), as was 2-year progression free survival, adjusted for age (76 vs. 61%; Prob> $\chi 2 = 0.0317$) [36].

In order to determine the effects of mEHT on CRT-related toxicity in HIV-positive participants, an analysis of the acute toxicity and quality of life of HIV-positive versus HIV-negative participants in the study by Minnaar et al. [35,36] was conducted. The effects of characteristics such as obesity on the frequency of adverse events in the study sample are included in this report. Quality of life (QoL) characteristics, such as physical well-being, can have an impact on clinical outcomes [37] and given the high morbidity associated with LACC, CRT treatment and with HIV-infection, QoL in the HIV-positive and HIV-negative participants in each treatment group is also reported.

Materials and methods

An ongoing phase III randomized controlled trial is being conducted at the Charlotte Maxeke Johannesburg Academic Hospital in Gauteng, South Africa, by the Radiation Sciences Department at the University of the Witwatersrand. The sample size calculation was based on the estimated required sample sizes for a two-sample comparison of survivor's functions at two years with a minimum sample size of 200 participants. A total of 271 patients were screened between January 2014 and November 2017, of which 210 were randomized for trial (see Figure 1). A stratified on-line software generated random-sampling tool supplied by the data management system, REDCap, was used to randomize participants to either the Control or mEHT Group; stratum: HIV status. Randomization accounted for age (<30 years; 30–50 years; >50 years), and International Federation of Gynecology and Obstetrics (FIGO) stage (IIB; IIIA and IIIB). The outcomes are the local disease control at six months post-treatment (reported by Minnaar et al. [35]) and 2-year survival. Approval has been obtained to follow participants for 5 years post-treatment. The 2- and 5-year follow-up period is ongoing and is expected to be completed in 2023. This analysis includes the 206 participants who arrived for treatment after randomization (mEHT Group: n = 105; Control Group: n = 101). Eligibility for the trial, as well as randomization and masking, are described previously [35].

Compliance with ethical standards

All procedures performed and work conducted in this trial involving human participants was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190295/M120477). The trial was registered on ClinicalTrials.Gov (ID: NCT03332069), and, as required by the institutional research committee, on the National Clinical Trials Register of South Africa (ID: 3012) before recruitment began.

Informed consent

All participants in the clinical trial described in this article have given written consent: to the inclusion of material pertaining to themselves; that they acknowledge that they cannot be identified via the article and that they have been fully anonymized in the report. The written consent obtained from all participants was approved by the institutional Human Research and Ethics Committee.

Treatment

All participants were planned to receive 50 Gy external beam radiation (EBRT) in 25 fractions, 24 Gy high dose rate (HDR) brachytherapy (BT) in three fractions (36 Gy equivalent dose in 2 Gy fractions

for an alpha-beta ratio of 10; source used: Iridium-192), and two doses of cisplatin (80 mg/m2) 21 days apart, not on mEHT or HDR BT days (subject to the participant's ability to receive cisplatin), as per institutional protocol. The EBRT target volume was planned and delivered to the whole pelvis using a four-field box technique on one of four Siemens linear accelerators in the department.

Two mEHT (Model: EHY2000+; Manufacturer: Oncotherm GmbH, Troisdorf, Germany) treatments were administered per week (maximum 10). mEHT was applied immediately before external beam radiation with a maximum of 30 min between the completion of mEHT and the completion of EBRT. This protocol was based on logistics and work-flow integration in the public hospital. A 30 cm electrode was used in the adjustable arm in order to cover as much of the pelvic field as possible. The treatment power was started at 60 W and increased using a step-up protocol over five minutes to the desired power of 90 W for the first treatment, 105 W for the second treatment, and a planned 130 W for the third and subsequent treatments (See Supplementary 1: hyperthermia schedule). Treatments were planned for a minimum of 55 min and a minimum energy dose of 360KJ per treatment. The first treatment is a safety treatment during which the participant is acclimatized to the treatment and the operator was able to identify potential risks. The first treatment is therefore administered at a low power without modulation.

Thermometry

It is recommended that thermometry be used to evaluate the efficiency of hyperthermia treatments [38,39], however this is associated with challenges such as increased cost and complexity, and the ability to heat uniformly and consistently regardless of tumor and patient characteristics [40]. Within the mEHT concept non-thermal (energy-dependent) effects are supposed to provide the dominant sensitization effect. As the temperature increase is limited and the temperature is not considered a key parameter in this concept, there is no need to measure it. Instead the applied dose of mEHT was controlled by measurement of the energy, which can be measured more easily and reliably [26,28,41]. This principle makes administering the treatments less complex and less costly and suggests that mEHT could be suitable for low-resource settings.

Outcome measures

Adverse events that occurred within 90 days of the start of RT were considered acute RT-related toxicity. The study utilized the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 from the National Cancer Institute (NCI) to define adverse events. The toxicity data was tabulated by treatment arm and HIV status. Thirty-nine adverse events from six categories (upper gastrointestinal (GIT); lower GIT; genitourinary tract (GUT); dermatologic and subcutaneous; neurological; hematological) at three time points (on treatment, six weeks and three months post-treatment) were analyzed. The frequency of all toxicities was reported and separate analyses for grade 3–4 toxicities for each system were conducted. Ototoxicity and peripheral neuropathy were grouped together under neurological toxicities, as these are both known to be potential cisplatin-related toxicities [42–44]. Adipose tissue burns, presenting as hard, painful, mobile masses within the adipose tissue, were classified according to the CTCAE v4.0 criteria under the heading 'Skin and subcutaneous tissue disorders—Other'.

QoL was measured at enrollment and again at six weeks, and three months post completion of treatment using the validated quality of life questionnaires (QLQ) C30 and Cx24, from the European Organization for Research and Treatment of Cancer (EORTC). Validated translations were available in English, Afrikaans, isiZulu, Sesotho, and isiXhosa [45]. The QLQ-C30 incorporates five functional

scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status, and perceived financial impact of the disease [46]. The QLQ Cx24 contains symptoms specific to cervical cancer and its treatment [47]. For the literate participants, the QLQ forms were provided in five different languages and the participants completed the forms themselves. For illiterate participants, nurses were asked to administer the forms and translate as needed. Nurses were blinded to the treatment group into which the participants were randomized. All scoring and reporting were done in accordance with the manual published by the EORTC which is made available with the QLQ forms.

Statistics

Chi-squared tests were employed to assess observed frequency differences of all toxicities in each treatment arm and by HIV status. Multivariate logistic regression models were used to determine predictors of outcomes such as the development of grades 3–4 toxicity.

For QoL, items were scored and analyzed according the EORTC scoring manual and were linearly converted to scores from 0–100 where a high score represents higher functioning or a higher symptom experience [48]. Unpaired t-tests were used to analyze differences in linear scores between the groups at each event. Paired t-tests were used to evaluate the changes in the linear scores between the groups.

Two-sided p-values are reported and p values <0.05 were considered significant. STATA 13.0 Statistics software program (Stata Corporation, College Station, TX), was used to analyze the data.

Role of the funding sources

The funding sources did not have any role in protocol design, data collection, analysis or reporting. The corresponding author had full access to all the data and was responsible for the final submission.

Results

The median age was 48.7 (range: 26.5–72.2 years), 63.6% of participants had stage III disease and 51% of participants were HIV-positive. Patient and treatment characteristics were evenly matched in both treatment groups as listed in Table 2.

Radiotherapy

The median time to complete RT was 41 days in both treatment groups with a range of 13–65 days in the mEHT group and 10–97 days in the control group. Reasons for taking in excess of 51 days to complete all RT include skin desquamation, bleeding and anemia, vomiting and dehydration and technical causes (such as machine services and repairs). The frequency of RT delays was significantly associated with HIV status ($\chi 2$: p = 0.020) with 12(11.4%) delays in the HIV-positive participants versus three (3%) delays in the HIV-negative participants (OR: 0.237; p = 0.030; 95% CI: 0.065–0.868). The association between treatment arm and RT delays was not significant with six out of 105(5.7%) in the mEHT group versus nine out of 101(8.9%) in the control group ($\chi 2$: p = 0.377; OR: 1.614; p = 0.381; 95% CI: 0.553–4.712).

Table 2. Characteristics of participants and treatment.

	mEHT 105	Control 101	*p*-value
HIV status			
Positive	52 (50%)	53 (53%)	
Negative	53 (50%)	48 (48%)	
FIGO staging			
IIB	40 (38%)	35 (35%)	
III	65 (62%)	66 (65%)	
Race			
African	97 (92%)	94 (93%)	
Caucasian	4 (4%)	1 (1%)	
Other	4 (4%)	6 (6%)	
Age (years)			
Mean	48.1	49.4	0.384
SD	10.8	10.3	
Range	26.5−68.9	28.4−72.7	
BMI			
Mean	27.8	27	0.387
SD	6.92	6.48	
Range	15−49	15−42	
Total RT dose			
Mean	84.7Gy	85.3	0.483
SD	7.61Gy	5.69	
Range	20Gy–86Gy	30−86Gy	
Treatment days			
Mean	41.6	42.8	0.255
SD	5.96	8.81	
Range	13−65	10−97	
Number of cisplatin doses			
Mean	1.37	1.28	0.323
SD	0.67	0.69	
0 doses	11 (11%)	14 (14%)	
1 dose	44 (42%)	45 (45%)	
2 doses	50 (48%)	42 (42%)	
CD4 count (cells/μL)			
Mean	586.1	525.1	0.242
SD	258.6	272.8	
Range	148−1204	95−1524	
No of mEHT doses			
Mean	9.26		
SD	1.65		
Range	1−10		
Average KJ administered during mEHT			
Mean	380.18		
SD	32.07		
Range	237.1−454.5		

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics; KJ: kilojoules; RT: radiation therapy; SD: standard deviation.

Table 3. Reasons for missed or delayed cisplatin.

	One dose		No cisplatin	
	mEHT	Control	mEHT	Control
Renal dysfunction	19	11	7	10
Delayed first dose[a]	10	7		
Leucopenia	0	0		
Noncompliant	2	0	1	1
Anemia	1	2	2	1
Missed dose	1	1		
Vomiting dehydration	1	0		
Deceased	1	1		
Sepsis	0	3		
Technical	0	3		
Too weak	0	1	0	1
Dehydration	0	1		
Low CD4 count			0	1
Total	35	30	10	14

[a]Reasons for delayed first dose were renal dysfunction (mEHT: $n = 1$; Control: $n = 1$), leucopenia (mEHT: $n = 2$; Control: $n = 1$), non-compliant (mEHT: $n = 0$; Control: $n = 1$), anemia (mEHT: $n = 4$; Control: $n = 4$), sepsis (mEHT: $n = 2$; Control: $n = 1$) and supply problems (mEHT: $n = 1$; Control: $n = 0$).

Cisplatin

Ten (9.5%) and 14 (13.9%) of mEHT and control group participants, respectively did not receive cisplatin. The mEHT group received a mean of 1.37 cycles and the control group received a mean of 1.28 cycles (p = 0.323) of cisplatin. The most common reasons for omission of the second cycle were renal dysfunction (mEHT: n = 19; Control: n = 11), followed by a delay in the administration of the first cycle (mEHT: n = 10; Control: n = 7). Table 3 lists the reasons for cancellation/omission of cisplatin.

In $\chi 2$ analyses, there were no significant associations between HIV status and number of cisplatin cycles (p = 0.549) or delays (p = 0.444) or between treatment arm and number of cisplatin cycles (p = 0.610) or delays (p = 0.575). HIV status was not a predictor of cisplatin dose delays (OR: 0.795; p = 0.452; 95%CI: 0.436–1.448), or cancelations (OR: 0.735; p = 0.474; 95%CI: 0.316–1.709). Likewise, the treatment group was not a predictor of cisplatin dose delays (OR: 1.180; p = 0.588; 95%CI: 0.648–2.150), or cancelations (OR: 1.504; p = 0.348; 95%CI: 0.641–3.530).

mEHT-specific toxicity

One hundred and five participants were treated with mEHT of which 102 (97%) were able to receive eight or more (≥80%) of the mEHT treatments. One participant had four treatments and two participants had six treatments. Of the three participants who received less than eight mEHT treatments, two had a Body Mass Index (BMI) over 25 and all three reported adipose burns, which was the cause for the reduction in the number of mEHT treatments.

Of the 105 participants treated with mEHT, 17(16.2%) reported adverse events: grade 1–2 adipose tissue burns (n = 10, 9.5%); grade 1 surface burns (n = 2, 2.0%) and pain (n = 9, 8.6%). Four (23.5%) of the participants with adverse events had a normal BMI and 13(76.5%) were overweight (BMI 25–29.9) or obese (BMI >30) [49]. A multivariate analysis showed that HIV status (OR: 1.47; p = 0.500; 95% CI: 0.480–4.512), increased BMI (OR: 1.78; p = 0.375; 95% CI: 0.499–6.335) and average energy (in Kilojoules) administered (OR: 0.986; p = 0.067; 95% CI: 0.98–1.00) were not significant predictors of adverse events associated with mEHT treatments.

A significant difference in grade 1–2 adipose burns between the treatment groups in the on-treatment analysis (mEHT: 10 out of 105(9.5%) compared to Control: 1 out of 101(1%); p = 0.023) was noted. This difference was not significant at six weeks or three months post-treatment.

Early toxicity analyzed by treatment group

The toxicities were analyzed by treatment group in order to determine if the addition of mEHT had any effect on the toxicity of either the chemotherapy or radiotherapy. Chi-squared frequency tables showed a significant association between the number of grade 1–2 neurological toxicities and the addition of mEHT (mEHT Group: n = 5(5%); control group: n = 0(0%); p = 0.030) at three months post treatment. The neurological toxicities reported were tinnitus (n = 1; HIV-positive), hearing loss (n = 2; one HIV-negative and one HIV-positive participant) and peripheral neuropathy (n = 3; all in HIV-negative participants). However, the significance of the association between treatment group and toxicity disappeared when the neurological toxicities were separated into peripheral neuropathy (p = 0.095) and ototoxicity (p = 0.174). Only one participant developed grade 3–4 neurological toxicity (HIV-positive, in the mEHT group, treated with cisplatin). There were no other significant associations between the treatment group and grade 1–2 or grade 3–4 toxicities. Supplementary 2 contains the results of the Chi-squared analyses comparing the grades 3–4 toxicities of each treatment group, and the grades 3–4 toxicities reported by HIV-positive compared to the HIV-negative participants.

Early toxicity analyzed by HIV status

There were some significant differences in specific symptoms associated with HIV status (diarrhea; creatinine clearance; vomiting and pigmentation); however, no clear pattern of association between the significant toxicities and mEHT treatments could be seen. At six weeks post treatment, HIV-negative participants reported a significantly higher frequency of grade 1–2 upper GIT symptoms, including nausea and vomiting (HIV-positive: n = 0(0%); HIV-negative: n = 4(4%); p = 0.044). No other significant associations were seen in our sample (see Supplementary 2).

Participants were then further analyzed by HIV status within each treatment group in order to identify any effect of mEHT on toxicity in HIV-positive participants. These results are shown in Table 4. In the mEHT Group, there were more grade 3–4 renal toxicities in the HIV-positive participants (n = 5) than in the HIV-negative participants (n = 0) on treatment (p = 0.027). In comparison, the control group had three HIV-positive (6%) and three HIV-negative participants (6%) who developed grade 3–4 renal toxicity (p = 0.900). Eight of the participants with grade 3–4 renal toxicities were HIV-positive and three were HIV-negative (p = 0.137) and the difference by treatment group overall was not significant (mEHT: n = 5(5%); Control: n = 6(6.3%); p = 0.707). In the control group there were significantly more grade 1–2 lower GIT toxicities on treatment reported in the HIV-positive participants (n = 28(53%) vs. n = 15(31%); p = 0.028). However, at six weeks post-treatment there were significantly more grade 1–2 upper GIT toxicities in the HIV-negative control group participants than in the HIV-positive control group participants (n = 0(0%) vs. n = 4(8%); p = 0.043).

Table 4. Frequency of grade 3–4 toxicities in each treatment group analyzed by HIV status.

	mEHT			Control		
	HIV-positive	HIV-negative	*p*-value	HIV-positive	HIV-negative	*p*-value
On treatment	*n* = 52	*n* = 53		*n* = 53	*n* = 48	
Hematologic	6 (12%)	6 (11%)	0.972	8 (15%)	6 (13%)	0.706
Neurological	1 (2%)	0 (0%)	0.310	0 (0%)	0 (0%)	
Lower GIT	0 (0%)	1 (2%)	0.320	0 (0%)	0 (0%)	
Upper GIT	0 (0%)	1 (2%)	0.320	0 (0%)	0 (0%)	
Dermatologic	3 (6%)	1 (2%)	0.299	1 (2%)	1 (2%)	0.727
Urogenital	3 (6%)	1 (2%)	0.299	1 (2%)	2 (4%)	0.500
Renal	5 (10%)	0 (0%)	*0.027**	3 (6%)	3 (6%)	0.900
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Six weeks	*n* = 48	*n* = 50		*n* = 48	*n* = 47	
Hematologic	0 (0%)	2 (4%)	0.162	3 (6%)	3 (6%)	0.979
Neurological	1 (2%)	0 (0%)	0.305	0 (0%)	0 (0%)	
Lower GIT	1 (2%)	0 (0%)	0.490	0 (0%)	0 (0%)	
Upper GIT	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Dermatologic	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0.320	
Urogenital	1 (2%)	0 (0%)	0.305	0 (0%)	2 (4%)	0.149
Renal	1 (2%)	0 (0%)	0.490	0 (0%)	0 (0%)	
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Three months	*n* = 45	*n* = 48		*n* = 43	*n* = 42	
Hematologic	3 (7%)	0 (0%)	0.069	1 (2%)	5 (12%)	0.085
Neurological	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Lower GIT	0 (0%)	1 (2%)	0.330	1 (2%)	2 (5%)	0.543
Upper GIT	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0.320	
Dermatologic	1 (2%)	0 (0%)	0.299	0 (0%)	0 (0%)	
Urogenital	1 (2%)	0 (0%)	0.299	1 (2%)	3 (7%)	0.294
Renal	3 (7%)	0 (0%)	0.069	1 (2%)	2 (5%)	0.543
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

GIT: gastrointestinal tract.
*Significant.

Multivariate regression analyses

In a multivariate regression analysis for the development of early toxicities in each system, HIV status, the number of cisplatin doses, and the treatment group, were tested for predictors of outcomes. These results are shown in Table 5. Seven participants developed grade 1–2 neurological toxicities, six of which were in the mEHT group, and the only participant to develop grade 3–4 neurological toxicities was also in the mEHT group. The odds of developing a neurological toxicity were therefore almost eight times higher in patients treated with mEHT (OR: 7.98; p = 0.053; 95%CI: 0.98–65.19). However, this was not a significant predictor of neurological toxicity development in the multivariate regression analysis, but cisplatin was a perfect predictor of the development of neurotoxicity, with all participants reporting neurotoxicity having received cisplatin. HIV-infection and receiving cisplatin were both significant predictors of the development of dermatological or subcutaneous early toxicities. Cisplatin was a significant predictor of renal toxicity (OR: 0.13; p < 0.005; 95% CI: 0.05–0.33) while HIV-status and the administration of mEHT were not significant predictors of renal toxicity.

Table 5. Regression analysis for overall acute toxicity by system.

Variable	Odds ratio [OR]	*p*-value	95% CI
Neurological			
HIV status	0.82	0.771	0.21–3.20
Cisplatin	All participants with neurological adverse events received cisplatin		
mEHT	7.98	0.053	0.98–65.19
Dermatologic/subcutaneous			
HIV status	2.61	0.033*	1.08–6.29
Cisplatin	3.54	0.016*	1.27–9.84
mEHT	1.35	0.485	0.58–3.11
Renal			
HIV status	0.58	0.098	0.30–1.12
Cisplatin	0.13	<0.005*	0.05–0.33
mEHT	0.95	0.887	0.50–1.82

*Significant.

Quality of life

There were no statistically significant differences in QLQ scores between the two groups at baseline assessment. At the 6-week time point the mean change in cognitive function in the mEHT group was significantly higher than in the control group. At three months post treatment, fatigue and pain were significantly reduced in the mEHT group (Table 6).

Table 6. Significant changes in the QoL results.

	mEHT group			Control group			
	Mean change	SD	95% CI	Mean change	SD	95% CI	*p*-value
Six weeks							
Cognitive function	13.6	33.1	6.97–20.24	3.5	30.6	2.89–9.85	0.031
Three months							
Social functioning	83.9	31.6	77.4–90.4	73.3	39.4	64.8–81.8	0.049
Emotional functioning	83.9	24.3	78.9–88.9	73.5	33.3	66.3–80.6	0.017
Fatigue	−13.6	26.0	−18.86 to −8.15	3.0	39.9	11.53–5.59	0.037
Pain	−21.0	33.0	27.76 to −14.18	−6.7	36.6	−14.62 to 1.05	0.007

SD: standard deviation.

At the three month time point there was an overall improvement in the mEHT group with significant improvements in: social functioning (mEHT: mean: 83.9, SD: 31.6, 95%CI: 77.4–90.4; Control: mean:

73.3, SD: 39.4, 95%CI: 64.8–81.8; p = 0.049), and emotional functioning (mEHT: mean: 83.9, SD: 24.3, 95%CI: 78.9–88.9; Control: mean: 73.5, SD: 33.3, 95%CI: 66.3–80.6; p = 0.017). The mean improvement in social, emotional and physical function at six weeks post-treatment was significantly higher (p = 0.0048; 0.0141 and 0.0155, respectively) in participants who had a complete response. Social-and emotional function continued to be higher in participants with a complete response at six months post-treatment (p = 0.0074 and 0.0035, respectively), as was the perception of body image (p = 0.0496). Supplementary 3 tabulates the significant improvements in QoL alongside the local control at six months post treatment.

Discussion

Models have shown that RF capacitive heating to deep pelvic tumors is not possible without severe adipose burns [50,51]. mEHT is a capacitive technology which has shown to increase the effectiveness of CRT in the management of LACC patients [35] despite the surprisingly low power output compared to other capacitive technologies. The cell killing effects of ionizing radiation are enhanced with the addition of mEHT at 41 °C to RT treatment regimens, as shown in preclinical [52] and clinical studies [35], and mEHT has shown to be cytotoxic at temperatures of only 38.5 °C [32,53]. Temperatures above 40 °C are not required during mEHT treatments as the dominant effect is non-thermal [32], allowing for a lower power output and for the treatment of deep seated cervical tumors [34,35], even in participants with a BMI of >27, with extremely low toxicity. These non-thermal effects are a result of the amplitude modulation.

In a theoretical model by Wust et al. [54], the temperature increase in the tumor during mEHT was not relevant and in clinical practice Lee et al. [33] demonstrated only mild temperature increases in cervical tumors treated with mEHT. The improved outcomes observed with the addition of mEHT to treatment protocols for cervical cancer [34,35] despite the low temperatures, corroborate the hypothesis that the dominant effects of mEHT may be non-thermal [32].

Although subcutaneous burns (grade 1–2) due to mEHT were significantly higher in the mEHT Group on treatment, these resolved by three months post-treatment and the overall dermatological and subcutaneous toxicity was not significantly different between the treatment groups. Subcutaneous adipose tissue is particularly sensitive to the effects of EBRT and exposure to radiation can lead to an alteration of the tissue's developmental potential [55] and fibrosis of the soft tissues is a known complication of EBRT [56]. It is therefore not unexpected that one participant in the control group presented with what appeared to be a subcutaneous burn at six weeks post-treatment. Our participants reported less subcutaneous toxicity than other studies using HT techniques in which a much higher power is applied. Additional thermometry to measure the skin temperature and prevent burns is therefore not necessary during mEHT, likely due to the effective cooling mechanisms and lower power output.

The development of neurotoxicity was more frequent in the mEHT Group however cisplatin was a perfect predictor of neurotoxicity in the multivariate regression analysis and was therefore the most likely cause of the development of neurotoxicity. Although peripheral neuropathy is a known but rare side effect of HT to the pelvis [5,17] and we therefore cannot exclude the potential effects of deep heating on the development of peripheral neuropathy related to increased local effectiveness.

In our participants treated with mEHT, the adverse events were less frequent and less severe than what is expected based on available literature [5,10,11,13,16,57], our participants could receive more

treatments (allowing for up to two treatments per week with a total of ten treatments), and the local control outcomes were significantly improved [35].

HIV

In our study, HIV infection was associated with an increased rate of RT delays; however, it was not a predictor of RT-related toxicities as reported in the literature [19,58,59]. The increased rate of renal toxicity in HIV-positive participants treated with mEHT, and decreased rate of renal toxicity in HIV-negative participants treated with mEHT, compared to the control group, is an unexpected result. Although the multivariate analysis showed cisplatin to be a significant predictor of renal toxicity, while HIV-status and treatment group were not significant predictors of renal toxicity, we suggest that renal function be closely monitored in HIV-positive patients treated with mEHT to the pelvis, combined with CRT.

All of our participants had either been on antiretroviral therapy (ART) for longer than six months or had a CD4 count above 200 cells/µL and this may have contributed to the improved outcomes and lower hematological toxicities seen in our HIV-positive participants, compared to reports in the literature. We did not observe significant differences in CRT or mEHT-related toxicity between HIV-positive and -negative patients, indicating that mEHT can be safely applied with CRT in HIV-positive patients. We did however observe an increase in upper GIT symptoms, such as vomiting, in the HIV-negative participants, which was also seen in a study analyzing the differences in CRT-related toxicities in HIV-positive (on ART; CD4 count >200 cells/µL) and HIV-negative cervical cancer patients in Zambia [60].

Temperature and thermometry

Thermometry in this study was not carried out as recommended with standard RF-capacitive heating or phased array heating techniques [61,62]. Thermometry is applied during HT treatments in order to provide a safety parameter and to predict effectiveness of the treatment. Various thermometry methods are available and have provided a large body of data, however the methods are expensive and demanding for the user. The power output [35] and temperatures reached during mEHT are lower than those achieved during conventional hyperthermia [33] and the toxicity associated with mEHT is not significant. The application of thermometry during mEHT is therefore not necessary as a safety parameter when treating cervical tumors.

As the treatment is effective, even under low temperatures and low power, the use of thermometry to predict effectiveness is not considered relevant during mEHT. The authors therefore suggest that the applied cumulative energy (power-on-time) might be more suitable as a dosing parameter during mEHT, as any non-thermal effects should be dependent on the exposure time of the amplitude-modulated RF.

Quality of life

These results show an improved functioning and symptom experience associated with the addition of mEHT and an improved QoL associated with local control. A complete response increases participant's ability to return to normal functioning status sooner, ultimately reducing the social burden of the disease.

Conclusion

The addition of mEHT applied at a low power of 130 W to CRT did not result in any unacceptable treatment-related toxicity in our high-risk (HIV-positive and partly obese) patient sample. The toxicities directly related to mEHT were mild and did not compromise the dose or timing of the cisplatin or RT. mEHT is therefore a safe adjunct to CRT protocols in HIV-positive participants and in a resource-constrained setting. This report is an important contribution to the field of knowledge in mEHT and provides important safety data for the use of mEHT in high risk populations, in the absence of sophisticated thermometry and planning technologies, providing evidence of the safety and efficacy of a technology that can easily be incorporated into general practices.

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Survival Outcomes of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy in Advanced Gastric Cancer

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Abstract

Background: Survival outcomes are still far from being satisfactory in patients with advanced gastric cancer, despite availability of novel chemotherapeutic regimens. **Aim:** This study evaluated the outcomes of patients with advanced gastric cancer who received chemotherapy along with additional treatment modalities targeting multiple tumor cell vulnerabilities. **Materials and Methods:** A total of 24 patients diagnosed with stage III–IV locally advanced or metastatic gastric adenocarcinoma that received metabolically supported chemotherapy (MSCT) combined with ketogenic diet, local hyperthermia, and hyperbaric oxygen therapy (HBOT) between April 2014 and October 2017 were included in this retrospective study. Survival outcomes were evaluated. **Results:** In 22 patients (88.0%), complete response was achieved. Mean duration of follow-up was 23.9 ± 12.7 months. Mean overall survival was 39.5 months (95% confidence interval [CI]: 28.1–51.0) and mean progression free survival was 36.5 months (95% CI: 25.7–47.2). No problems were encountered due to fasting, hypoglycemia, ketogenic diet, hyperthermia or HBOT. **Conclusions:** The combination treatment used in this study (MSCT together with a ketogenic diet, hyperthermia and HBOT) appears to be promising in the treatment of advanced gastric cancer. Further research and comparative clinical trials are warranted to support and standardize this novel treatment protocol.

Keywords: *Advanced gastric cancer, hyperbaric oxygen therapy, hyperthermia, ketogenic diet, metabolically supported chemotherapy*

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Introduction

Gastric cancer represents a global health problem with substantial mortality and morbidity burden. In 2012, almost one million new cases were diagnosed with gastric cancer and >700,000 died.[1]

Surgery provides high cure rate for early stage disease (stage IA/B), but these patients represent a minority of the cases. Almost 80%–90% of patients are either diagnosed at an inoperable stage or develop recurrence after curative surgery; and patients with advanced disease with inoperable, recurrent or metastatic tumors have poor prognosis, even poorer without chemotherapy.[2] Currently, chemotherapy is the mainstay of treatment in advanced gastric cancer, although there is no consensus on the ideal regimen.[2]

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The recent ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up of gastric cancer recommends doublet or triplet platinum/fluoropyrimidine combinations for fit patients with advanced/metastatic disease as first line treatment.[3] In addition, encouraging results have been obtained with regimens consisting of oxaliplatin, leucovorin, and 5-FU in patients with advanced gastric cancer.[4-12] However, the survival outcomes are still far from being satisfactory in this group of patients with poor outlook.

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In cancer cells, aerobic fermentation compensates for insufficient oxidative phosphorylation, a phenomenon first described by Otto Warburg who hypothesized that "cancer is a disease of metabolic dysregulation."[13,14] This abnormal energy metabolism characterized by glucose dependency and increased lactate production has been linked to mitochondrial dysfunction and genetic mutations.[15,16] Metabolically supported chemotherapy (MSCT) is a novel chemotherapy administration strategy targeting this metabolic difference of cancer cells.[17-19] In an attempt to increase membrane permeability for chemotherapeutic agents[20] and to develop mild hypoglycemia resulting in an acute metabolic stress on cancer cells, MSCT integrates 12-h fasting before each chemotherapy session and concomitant administration of insulin to the usual chemotherapy schedule. An additional approach to target glucose dependency of cancer cells is the adaption of a ketogenic diet, which has been shown to slow the progression of cancer.[19,21-25]

Hyperthermia causes direct cytotoxicity and has the potential to sensitize cancer cells to radiotherapy and chemotherapy as evidenced by previous studies.[17,19,26-30] Hyperbaric oxygen therapy (HBOT) involves the administration of oxygen at an elevated pressure resulting in better oxygenation of tissues. It has the potential to counteract unfavorable effects of hypoxia during chemotherapy and radiotherapy.[31-34] Several clinical studies demonstrated its benefit when used in combination with chemotherapy and radiotherapy for the treatment of various malignancies.[26,27,35]

MSCT, ketogenic diet, hyperthermia, and HBOT seem to have a synergistic action since they target overlapping metabolic pathways and vulnerabilities of cancer cells. Combination of these four modalities may prove more efficient when compared to chemotherapy alone. To date, no study has examined the role of this novel combinatorial therapeutic strategy in the management of gastric cancer.

This study aimed to evaluate the survival outcomes of patients with advanced gastric cancer who received MSCT with triplet taxane/platinum/fluoropyrimidine combination together with ketogenic diet, hyperthermia, and HBOT.

Materials and Methods

Study design and patient selection

This retrospective single-center study included 24 patients diagnosed with stage III–IV locally advanced or metastatic gastric adenocarcinoma that received MSCT combined with ketogenic diet, local hyperthermia and hyperbaric oxygen therapy between April 2014 and October 2017. The above-mentioned combination treatment used in this study is the routine treatment approach adopted in our clinic. Eligible patients were identified from the institutional database through screening of medical records of all patients diagnosed with gastric cancer (any class, stage, or subtype) and treated at our clinic during the study period; and the data were extracted retrospectively. Inclusion criteria were as follows: Biopsy-proven gastric cancer, measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1),[36] radiologically proven stage III-IV disease, and receiving study treatment during the study period.

Study treatments

All patients were advised to adapt a ketogenic diet throughout the treatment period. Before each metabolically supported chemotherapy session patients fasted overnight and immediately before chemotherapy administration they received regular insulin (Humulin®R) in doses ranging between 5 and 20 IU (in order to achieve a state of mild hypoglycemia with blood glucose levels around 50–60 mg/dL for normoglycemic patients and in accordance with previous MSCT protocols).[17-19] All patients were administered a chemotherapy regimen consisting of docetaxel 25 mg/m^2 (over 60 min), carboplatin AUC 2 (over 30 min and subsequent to docetaxel), and 5-FU 600 mg/m^2. This combination treatment was administered in an outpatient setting and repeated on the first and eighth day of every three-week cycle until disease progression. Following progression, patients were administered a chemotherapy regimen consisting of oxaliplatin 85 mg/m^2 IV over 2 h on day 1 plus leucovorin 400 mg/m^2 IV over 2 h on day 1 plus 5-FU 400 mg/m^2 IV bolus on day 1, then 1,200 mg/m^2/day for 2 days (total 2,400 mg/m^2 over 46–48 h) continuous infusion, repeated every 2 weeks as second-line treatment. Patients received maintenance therapy with their latest regime until death as long as they tolerate.

After each chemotherapy session, patients received 60-min of local hyperthermia application and 60 min of hyperbaric oxygen therapy. For each hyperthermia session, OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany) was used to gradually increase the temperature of the tumoral region to 45°C with a mobile electrode. Quamvis 320 hyperbaric oxygen chamber (OxyHealth, CA, USA) was used to produce an operating pressure of 1.5 atmospheres absolute (ATA) in each HBOT session.

Assessment of response

Assessment of treatment response was based on radiographic evaluations at the end of each 3-month period and was done by PET-CT. In patients with complete response based on PET-CT scan, confirmatory endoscopic evaluation was also done.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were presented in number (percentage), median (range), mean (95% confidence interval), where appropriate. The

time between the date of diagnosis and death from any cause was defined as overall survival. Progression-free survival was defined as the time frame between the date of diagnosis and death from any cause or progression. Patients without event at the last follow-up were censored. Kaplan–Meier analysis was used to estimate survival rates and intergroup comparisons were performed using log-rank test. Level of statistical significance was set at $P < 0.05$.

Results

Patient characteristics are shown in Table 1. Majority of the patients (75.0%) had metastatic disease and more than one-third had relatively poor performance status (ECOG status ≥2). In 22 patients (88.0%), PET-CT showed complete response at follow-up and this was confirmed by the endoscopic and histological absence of tumor (in blind biopsies) in all patients. In three patients, partial response could be achieved (12.0%). Seven patients received surgical treatment (29.2%). Three of them (12.5%) had surgery before chemotherapy and considered to be at advanced stage based on intraoperative or histopathological findings. The remaining four (16.7%) had surgery after complete response to chemotherapy.

Table 1: Patient characteristics

Characteristic	*n*=24
Age, year, median (range)	54 (32-76)
Male gender	14 (58.3%)
Disease extent	
Metastatic (stage IV)	18 (75.0%)
Locally advanced (stage III)	6 (25.0%)
ECOG status	
I-II	15 (62.5%)
III	9 (37.5%)
Histology	
Adenocarcinoma	9 (37.5%)
Signet ring cell carcinoma	15 (62.5%)
Radiotherapy	12 (50.0%)
Surgery	7 (29.2%)

Unless otherwise stated, data presented as *n* (%). ECOG=Eastern Cooperative Oncology Group

During the mean duration of follow-up of 23.9 ± 12.7 months (median 22.2, range 8.6–63.5 months), 9 patients died. Mean overall survival was 39.5 months (95% confidence interval [CI]: 28.1–51.0) and mean progression free survival was 36.5 months (95% CI: 25.7–47.2). Figure 1 shows Kaplan–Meier curves for overall survival and progression free survival.

Table 2 shows mean overall survival and mean progression-free survival by patient characteristics. None of the patient characteristics, including age, gender, disease extent, performance status, histology or additional treatments, had any effect on overall survival or progression free survival.

Table 2: Survival rates by patient characteristics

Characteristic	Mean OS Months (95% CI)	*P**	Mean PFS Months (95% CI)	*P**
All patients (*n*=24)	39.5 (28.1-51.0)		36.5 (25.7-47.2)	
Age				
≤Median (*n*=12)	41.7 (25.2-58.2)	0.735	39.3 (22.8-55.7)	0.701
>Median (*n*=12)	29.4 (24.4-34.4)		27.4 (22.1-32.8)	
Gender				
Male (*n*=14)	33.2 (25.9-40.5)	0.925	32.3 (24.3-40.3)	0.700
Female (*n*=10)	42.6 (22.6-62.6)		38.0 (20.4-55.6)	
Disease extent				
Metastatic (*n*=18)	35.7 (23.9-47.5)	0.318	32.3 (21.2-43.4)	0.204
Locally advanced (*n*=6)	41.3 (32.7-49.9)		40.9 (31.7-50.2)	
ECOG status				
I-II (*n*=15)	46.2 (31.5-60.9)	0.675	44.8 (30.9-58.6)	0.420
III (*n*=9)	31.9 (24.0-39.8)		29.1 (21.1-37.1)	
Histology				
Adenocarcinoma (*n*=9)	35.6 (26.8-44.5)	0.608	31.9 (22.3-41.5)	0.992
Signet ring cell carcinoma (*n*=15)	39.5 (25.2-53.9)		37.7 (23.4-52.0)	
Surgery				
Surgery (*n*=12)	39.9 (29.8-49.9)	0.331	39.8 (29.8-49.9)	0.220
No surgery (*n*=12)	36.7 (24.2-49.2)		32.9 (21.2-44.6)	
Radiotherapy				
Radiotherapy (*n*=7)	33.7 (28.2-39.2)	0.246	31.7 (25.6-37.8)	0.369
No radiotherapy (*n*=17)	35.3 (23.3-47.4)		33.3 (21.3-45.3)	

*Log-rank test

*Significance was set at $P < 0.05$. OS=overall survival; PFS=progression-free survival; ECOG=Eastern Cooperative Oncology Group

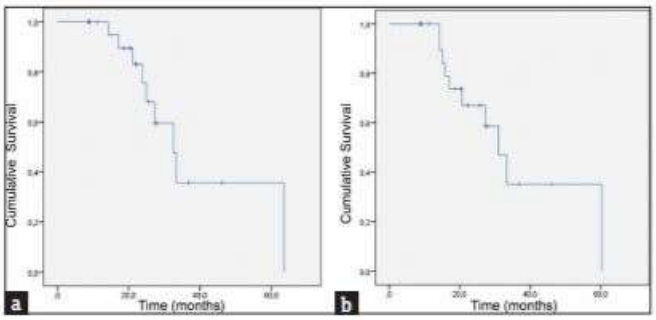

Figure 1: Kaplan–Meier curves for overall survival (a) and progression-free survival (b) – all patients. *P* values are calculated with log-rank test

During the study period, no problems were encountered due to fasting, hypoglycemia, ketogenic diet, hyperthermia, or hyperbaric oxygen therapy.

Discussion

This study integrated additional modalities targeting multiple susceptibilities of tumor cells into a chemotherapy schedule in patients with advanced gastric cancer and obtained promising results in terms of survival outcomes. To the best of our knowledge, this study is the first to examine the efficacy of a chemotherapy schedule administered in a metabolically supported fashion, together with ketogenic diet, hyperthermia, and HBOT, in patients with advanced gastric cancer.

A recent meta-analysis compared triplet versus doublet chemotherapy as a first-line treatment in patients with advanced esophagogastric cancer.[37] Triplet chemotherapy was associated with superior survival and response outcomes, despite increases in grade 3–4 thrombocytopenia, infection, and mucositis risks.[37] In that meta-analysis, reported overall survival rates ranged between 9.2 and 14.6 months in the arms of patients that received triplet combinations with taxane, platinum, and fluoropyrimidine. Among them, the largest V325 study reported 9.2 months of overall survival in the arm of docetaxel and cisplatin plus fluorouracil,[38] which is similar to the chemotherapy regimen administered in the present study. In addition, a recent study included advanced gastric cancer patients with good performance status (0–1) to test the efficacy and tolerability of docetaxel and cisplatin plus S-1 combination as a first-line chemotherapy and obtained median progression free survival and overall survival of 6.5 and 15.5 months, respectively.[39] In this study, a taxane, platinum, and fluoropyrimidine-based combination was administered as a first-line treatment to advanced gastric cancer patients with relatively poor outlook (75% having distant metastasis and more than one-third with ECOG PS ≥2) and encouraging survival outcomes were obtained (mean overall survival, 39.5 months; mean progression free survival 36.5 months) during a mean follow-up period of 2 years. However, median survival could not be reached since >60% of the patients were alive at the time of last evaluation. These promising findings may be attributed to the possible contribution of metabolically supported administration and additional modalities targeting multiple susceptibilities of the tumor cell included in the present study, which merit further investigation in large comparative trials.

To the best of our knowledge, only a few studies have reported on the use of MSCT in several malignancies: A retrospective clinical study and two case reports. A recent study in patients with unresectable ductal pancreatic adenocarcinoma examined the efficacy of standard gemcitabine-based and/or FOLFIRINOX protocol administered in a metabolically supported fashion and reported a median survival of 19.5 months for these patients with poor expected outcome.[17] FOLFOX6 regimen administered using MSCT approach in an elderly patient with locally advanced rectal cancer provided complete clinical and pathological response,[18] and an MSCT regimen combining docetaxel, doxorubicin, cyclophosphamide in a an overweight 29-year-old woman with stage IV (T4N3M1) triple-negative invasive ductal carcinoma of the breast provided complete clinical, radiological, and pathological response.[19]

Previous studies provided evidence on potential mechanisms through which metabolic support to chemotherapy may exert its beneficial effects. Both insulin itself and the resultant induced hypoglycemia seem to have role. Induced hypoglycemia targets the dysregulated metabolism and glucose dependency of the tumor cell.[13-16,40] Low availability of circulating glucose would pose an acute metabolic stress and probably improve cytotoxicity of the chemotherapeutic agent. Insulin itself has the potential to increase membrane permeability to chemotherapeutics, thereby increasing their availability for the tumor cell, through the formation of drug–insulin complexes.[41-45] In addition, number of insulin and insulin-like growth factor (IGF) receptors is higher on tumor cells when compared to healthy cells.[46,47] Reaction between insulin and these receptors has the potential to extend the S-phase and render cancer cells more susceptible to the cytotoxic effects of chemotherapeutics for longer periods,[48] while relatively sparing healthy cells, thereby improving safety and tolerability.

Ketogenic diet, another component of our combination treatment also targets metabolic dysregulation of tumor cells and possibly exerts its action through lowering the level of available circulating glucose. To date,

several preclinical studies and case reports provided support for its potential adjunctive use in the treatment of malignant conditions.[19,21-25,49-54] Hyperthermia, exploits heat sensitivity of cancer cells and causes direct cytotoxicity, and HBOT target the reliance of tumor cells on glycolysis, a major contributor to the upregulation of antioxidant activity responsible for the increased resistance of the tumor to pro-oxidant chemotherapy and radiation therapies.[55] The synergism observed in various combination of these therapies (ketogenic diet, hyperthermia, HBOT) and their benefits in increasing the efficacy of conventional therapies have already been reported in a number of studies studying various malignant conditions.[15,19,24-29,35,56,57] Among them, the study by Ohguri *et al.* added hyperthermia and HBOT to carboplatin/paclitaxel chemotherapy in NSCLC patients with multiple pulmonary metastasis and obtained promising results (an objective response in almost two-thirds of the patients).[26] In addition, a recent study evaluated the effect of administration of all these three modalities along with MSCT in stage IV triple negative breast cancer patient with complete response.[19] This study also used all three modalities in addition to MSCT and targeted multiple vulnerabilities at metabolic, cellular and pharmacological level, which explains the high survival rates obtained.

Finding of this study, along with previous pre-clinical and clinical evidence, implies that adding modalities to complement conventional treatment may prove beneficial in many malignant conditions, provided that they target multiple vulnerabilities of tumor cells in an attempt to augment the efficacy and specificity of chemotherapeutic agents. Further research is warranted.

Retrospective design and the lack of a control group are the major limitations of this study. A randomized trial design would provide more robust evidence. In addition, relatively small sample size could have prevented to achieve power sufficient to detect survival differences between subgroups. Larger clinical studies with prospective design would further clarify the potential benefits of this treatment combination.

Conclusion

The combination treatment used, in this study (MSCT together with a ketogenic diet, hyperthermia and HBOT) is promising in the treatment of advanced gastric cancer. Further research and comparative clinical trials are warranted to support and standardize this novel treatment protocol.

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Conflicts of interest

There are no conflicts of interest.

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Putative Abscopal Effect in Three Patients Treated by Combined Radiotherapy and Modulated Electrohyperthermia

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Purpose: True abscopal responses from radiation therapy are extremely rare; the combination of immune checkpoint inhibitors with radiation therapy has led to more reports of the abscopal effect, but even in this setting, the genuine magnitude remains unknown and is still considered generally uncommon. We report the occurrence of what appears to be putative, durable abscopal tumor responses with associated auto-immune systemic reactions resulting from the combination of local radiotherapy (RT) and modulated electrohyperthermia (mEHT).

Materials and Methods: Data from advanced cancer patients treated palliatively with RT and mEHT between January and December 2017 were collected as part of a post-marketing safety monitoring program of mEHT therapy. We specified a minimum RT dose of 30 Gy and at least four mEHT treatments for reporting toxicities, which was the primary aim of the larger study.

Results: Thirty-three patients treated with RT and mEHT, both applied to the same lesion, were included. The median RT dose was 45.5 Gy in 20 fractions (fxs) and the median number of mEHT treatments was 12 (range, 4–20). Most patients had subsequent systemic therapy after one course of RT and mEHT. Three patients (9.1%) developed autoimmune toxicities. Case number 1 received RT and mEHT only; case number 2 had two cycles of concurrent low dose chemotherapy during RT; and case number 3 received concurrent immune checkpoint inhibitors. None of the three patients received any further systemic treatment due to obvious treatment-related autoimmune reactions which occurred rapidly after RT; one had autoimmune hepatitis, one had dermatitis herpetiformis and the third developed severe myasthenia gravis. Interestingly, what we surmise to be long-lasting abscopal responses outside the irradiated area, were noted in all three patients.

Conclusion: RT combined with mEHT could putatively result in enhancing immune responsiveness. These preliminary observational findings lead to the generation of a hypothesis that this combination induces both an in-situ, tumor-specific immune reaction and an anti-self-autoimmune reaction, in at least a small proportion of patients, and of those who experience the auto-immune response, tumor response is a concomitant finding. Mechanisms underlying this phenomenon need to be investigated further.

Keywords: modulated electrohyperthermia, immunotherapy, radiotherapy, abscopal effect, immune-related adverse events

Introduction

Local hyperthermia (HT) has long been regarded as an effective radio-sensitizer (1). Modulated electrohyperthermia (mEHT) therapy is one form of hyperthermia (2). mEHT utilizes the biophysical differences between malignant and normal cells for cancer-cell specific selective energy deposition, believed to be due to the lower impedance on the transmembrane protein clusters of malignant cells (3). The modulated electromagnetic frequency spectrum of 13.56 MHz from mEHT is similar to the alternating electrical field generated from tumor treating field therapy (TTField, Novocure, Inc.) (4–6). mEHT applies lower power than conventional HT, thus interstitially measured average temperature is relatively low, around 39.5°C. However, the corresponding transmembrane temperature differential across a cell is often quiet high (7). This transmembrane thermal stress destabilizes cell membranes, resulting in necrosis, and also enhanced apoptosis (8–11). This effect has been shown to enhance the release of heat shock proteins (HSPs), produce damage-associated molecular patterns (DAMP) and leads to increased immunogenicity, thereby mediating immunogenic cell-death (12). The electric field effect has also been demonstrated to activate intensive lymphocytic and dendritic cell penetration into tumor (13).

The abscopal effect from radiotherapy (RT) has been known for a long time and was interpreted as an immune-mediated effect (14). Despite millions of patients having been treated with RT, only 46 abscopal cases induced by radiation treatment alone have been described between 1969 and 2014

(15). In preclinical models, the combination of immune check point (ICP) inhibitors with RT has demonstrated abscopal effects, but human reports still remain sparse, largely restricted to melanoma and non-small cell lung cancer (16–21). However, in all such reports, it remains difficult to ascribe the abscopal effect purely to RT alone or in combination with immune enhancing therapeutics (22). A prospective trial of RT, with a granulocyte-macrophage colony stimulating factor in metastatic diseases, reported a surprisingly high abscopal effect of 27.6% (23). RT creates tumor and normal tissue damage, lysis, and antigen release for sustained in-vivo vaccination events. Thymus-derived regulatory T (Treg) cells played a critical role in the control of immune tolerance to self-antigens, however, they also resulted in reduced anti-tumor immunity (24). There were very few literature reports on how therapy related autoimmunity-mediated antitumor activity (25, 26).

We speculated that the incidence of the abscopal effect may be higher in patients who develop autoimmunity. Bakacs et al. reported that immune related adverse events (irAEs) induced by ipilimumab are very similar to the chronic graft vs. host disease that ensues allogenic bone marrow transplantation (27). Autoreactive T cells may bypass the negative selection pressure in the microenvironment of the tumor and differentiate to memory T cells that recognize both "self" and "tumor." We report, we believe for first time, that patients treated with RT and mEHT may have a long treatment-free period once they unleash an autoimmune reaction, and further, that in such patients, successful salvaging through low-dose ICP inhibitors may be possible at tumor recurrence.

Materials and Methods

We performed a single institution, observational case-cohort study for patients with metastatic cancers of various origins, treated with a combination of RT and mEHT, with a minimum RT dose of 30 Gy and at least four mEHT treatments, to report unexpected adverse events. This retrospective analysis was conducted as part of a post-marketing safety surveillance program after the approval of the mEHT device in the class III medical category in Taiwan. The study was approved by the Institutional Review Board and was conducted according to the guidelines of Good Clinical Practice.

Patient Selection

Enrolled patients were 20 years of age or older, presented with inoperable, recurrent, or metastatic diseases, requiring palliation with RT. In our study, all patients underwent concurrent RT and mEHT with or without systemic therapies, based on the underlying clinical condition. All institution-specific consent requirements were adhered to; written informed consent was obtained from the participants for the publication of the case series.

Radiotherapy

RT was performed using conventional fractionation (and not hypofractionated) schedules, with a dose of 2 to 3.5 Gy per fraction (fx), five times per week to at least 30 Gy, as clinically appropriate and necessary. The clinical target volume (CTV) was defined as the gross tumor volume (GTV) plus a margin of 3–5 mm, based on the specific tumor type being addressed. Patients were treated with Elekta Synergy® (Elekta, Stockholm, Sweden) or TomoTherapy® (Accuray, Sunnyvale, CA, USA) with standard immobilization devices, using image-guided, modulated arc therapy with 6-MV photons for most of the patients. For patients who had received RT prior to the study, the original treatment plans were retrieved in every case of suspected overlap with the prior RT fields, and appropriate organ-at-risk constraints were adhered to.

Hyperthermia (mEHT)

The mEHT treatment was applied using an EHY 2000+ hyperthermia device (OncoTherm GmbH, Germany). Treatment lasted for 60 min and was administered once weekly. A 30 cm in diameter

circular electrode was placed at the irradiated tumor site, approximating placement at the radiation field isocenter. A 13.56 MHz radiofrequency (RF) was used with a real-time, automatic tuning device resulting in energy-transfer matching and ensuring a standard wave ratio of ~1 (the most ideal value). The power was initially set to 80 Watts (W) and a step-up protocol was applied to increase by 20–30 W every 5 min, until 150 W was reached for the remaining treatment duration. The goal for the target energy delivered was minimally set at 500 kJ per treatment. All appropriate vital sign monitoring during and after treatment was conducted as per standard practice. With this technique, intratumoral temperature measurement is typically not performed because the temperature elevation measured by a conventional thermocouple is usually <2°C (28). Adverse events were assessed throughout each treatment, which included heat sensitivity, skin burning, pain, and gastric discomfort.

Outcomes Evaluation

The primary endpoint was toxicity, which was evaluated weekly and recorded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. during the RT and mEHT period and 2 months after. The secondary outcome was the radiologic response, which was evaluated on the irradiated lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (29) every 3 months with CT, PET-CT, or tumor markers, based on a baseline selection diagnostic/imaging finding. The response categories of interest included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Most patients received some kind of systemic treatment afterward. The length of follow-up was defined from the last day of RT to the last follow-up visit. Baseline measurements and changes in the neutrophil to lymphocyte ratio (N/L) before and after treatment were collected.

Statistical Analysis

The impact of patient-, tumor-, and treatment-related factors on response was evaluated using a univariate and multivariable analysis. Survival curves were estimated using the Kaplan-Meier method. Fisher's exact test (two-tailed test) was used for evaluating 2 × 2 tables for significance. Statistical analyses were performed with the SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). $P < 0.05$ were set for statistical significance.

Results

Patient and Disease Characteristics

Thirty-three patients with recurrent or metastatic cancer was enrolled between January 2017 and December 2017. Patient characteristics are listed in Table 1. The median patient age was 59.3 years (range, 38–84 years). Breast cancer, lung cancer, hepatoma, cholangiocarcinoma, and urothelial carcinoma were the five most common disease entities. The thorax was the most commonly treated site (12 patients in total, including four lung cancer patients and eight for breast cancer) followed by abdomen (nine patients) and liver (six patients). During the RT and mEHT treatment, 16 patients received concurrent chemotherapy, nine had ICP inhibitors and six were treated with both agents. The median follow-up time was 11.6 months (range, 4–22.7 months) with no patients lost for follow-up.

Characteristics	No.	%
Sex		
Female	17	51.5
Male	16	48.5
Age, median, range, years	59.4	38–84 years-old
Disease entities		
Breast cancer	8	24.4
Lung cancer	4	12.1
Hepatocellular carcinoma	3	9
Cholangiocarcinoma	3	9
Urothelial carcinoma	3	9
Others	12	36.5
Treatment before RT+ mEHT		
Surgery	12	36.3
RT	19	57.6
ChT (include hormone, target therapy)	21	63.6
IO	0	0
Cht+IO	2	6
Treatment during RT+ mEHT		
ChT (include hormone, target therapy)	16	48.5
IO	9	27.2
ChT+IO	6	18.2
Treatment after RT+ mEHT		
Surgery	1	4.6
ChT (include hormone, target therapy)	13	59.1
IO	3	13.6
ChT+IO	5	22.7

Cht, chemotherapy; IO, immune-Oncology.

Table 1. Patient characteristics.

Treatment

The median RT dose was 45.5 Gy (range, 30–66 Gy), and the mean GTV was 138.9 cm3 (ranged between 20 and 5064.7 cm3). The median number of mEHT treatment fractions was 12 (range, 4–20).

Treatment Outcome and Toxicities

The combination of RT and mEHT treatment was well-tolerated. A full listing of adverse events during the RT plus mEHT treatment is provided in Table 2. Common treatment-related adverse events were grade 1 skin, and grade 2 myelotoxicities. Transient core body temperature elevation (>38°C), which resolved shortly after mEHT treatment, was noted in six patients; two obese patients had localized subcutaneous fat induration that persisted for several weeks, and then resolved. The most important adverse events that went beyond our expectation were autoimmune related toxicities (three out of 33 patients, 9.1%). One patient treated only with RT and mEHT developed grade 3 autoimmune hepatitis. One patient who was simultaneously treated with low-dose ICP (Yervoy® and Opdivo®) developed grade 3 myasthenia gravis, and another patient developed grade 2 autoimmune-related skin toxicity (dermatitis herpetiformis). All three patients who developed

autoimmune toxicities had long lasting abscopal effects in the absence of any further subsequent systemic treatment.

Treatment toxicity (CTCAE v4.0)

Toxicity	Case number (*N*)	%
Skin toxicity		
Grade 0	20	60.6
Grade 1	12	36.3
Grade 2	1*	3.1
Grade 3	0	0
Hepatic toxicity		
Grade 0	31	93.8
Grade 1	1	3.1
Grade 2	0	0
Grade 3	1**	3.1
Myelotoxicity		
Grade 0	24	72.7
Grade 1	1	3.1
Grade 2	6	18.2
Grade 3	2	6.0
Neurotoxicity		
Grade 0	32	96.6
Grade 1	0	0
Grade 2	0	0
Grade 3	1***	3.1
Nausea and vomiting		
Grade 0	30	90.9
Grade 1	1	3.1
Grade 2	2	6.0
Grade 3	0	0
Diarrhea		
Grade 0	30	90.9
Grade 1	1	3.1
Grade 2	2	6.0
Grade 3	0	0
Elevated core body temperature (after treatment)		
Yes	6	18.2
No	27	81.8
Fat induration		
Yes	2	6.0
No	31	94.0

**Autoimmune reaction: Dermatitis herpetiformis.*
***Autoimmune reaction: Autoimmune hepatitis.*
****Autoimmune reaction: Myasthenia gravis.*

Table 2. Treatment toxicities during RT + mEHT.

Among the in-field evaluable lesions treated with RT and mEHT (39 lesions in 33 patients), CR, PR, SD, and PD were observed in 6.1, 54.5, 27.3, and 12.1% of patients (Table 3). All eight breast cancer patients had ≧PR response. Somewhat surprisingly, larger tumors (>500 ml) demonstrated superior responses than smaller tumors (<500 ml) (100 vs. 48%, p = 0.012) (Table 3). All the patients with autoimmune toxicities had a tumor size of more than 500 ml. Because of the small sample size, multivariate analysis failed to show significant differences between response and age, tumor size, number of mEHT treatments, tumor depth, the use of ICP inhibitors, chemotherapy, and autoimmune reactions. Thirteen patients (39.4%) had a decreased N/L ratio 1 month after RT + mEHT, which includes two patients with CR, six with PR, three with SD and two with PD (Table 3). The three patients with an autoimmune abscopal effect had an elevated N/L ratio before treatment (>8) which decreased to <3.5 after treatment. The median survival time was 11.4 months (range, 2.6–16.9

months) in patients whose N/L decreased, vs. 8.9 months in patients with elevated N/L (range, 1.7–16.2 months).

Response	Metastatic/recurrent (*N* = 33)	GTV ≥500 ml (*N* = 8)**	GTV <500 ml (*N* = 25)	Decreased N/L ratio post treatment (*N* = 13)****	Increased N/L ratio post treatment (*N* = 20)
CR	2 (6.1%)			2	0
VGPR*	5 (15.2%)	8*** (100%)	12 (48%)	3	2
PR	13 (39.4%)			3	10
SD	9 (27.3%)	0 (0%)	13 (52%)	3	6
PD	4 (12.1%)			2	2

*VGPR, Very good partial response defined as >90% regression.
**p = 0.012 Fisher's exact test.
***The 8 patients with large tumors included 3 patients with autoimmune toxicities including 1 CR (urothelial carcinoma); 1 VGPR (breast cancer), 1 PR (cholangiocarcinoma). Another 5 patients included 1VGPR (hepatoma) and 4 PR (1 cervix and 3 breast cancers).
****p = 0.245 Fisher's exact test.

Table 3. Response rate of the irradiated sites.

Case Presentation: Autoimmune Phenomena Associated With Abscopal Tumor Response

Case 1

A 42-year-old female patient presented with a left breast ulcerative fungating mass (>10 cm) with palpable bilateral axillary lymph nodes. She was diagnosed with metastatic, left breast, triple-negative invasive ductal carcinoma. She refused chemotherapy and received palliative RT consisting of 50 Gy in 25 fxs plus weekly mEHT for six treatments. Elevated serum alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase and bilirubin was identified 2 weeks after RT. Positive anti-microsomal antibody and anti-smooth muscle antibody levels assisted in making a diagnosis of autoimmune hepatitis. She was treated with prednisone (starting at 40 mg daily and tapered to 10 mg daily within 4 weeks). The primary tumor shrank rapidly to ~1 cm 1 month after treatment and a wide excision was performed 2 months later (Figure 1A). The bilateral axillary and the left internal mammary metastatic lymph nodes outside the local treatment field demonstrated dramatic and sustained regression, qualifying for our abscopal response criteria. More than 1 year later, she developed lung metastases and was treated bi-weekly with reduced-dose ICP inhibitor treatment (60 mg of Opdivo®) for two doses with a significant response (Figure 1B), resulting in a CR. Subsequently, her serum AST, ALT, and bilirubin levels increased once again, suggesting relapse of her autoimmune hepatitis, resulting in discontinuation of immunotherapy (Figure 1C). Despite this, her lung metastases demonstrated sustained remission, and she is still alive and tumor-free, >12 months after discontinuing ICP therapy.

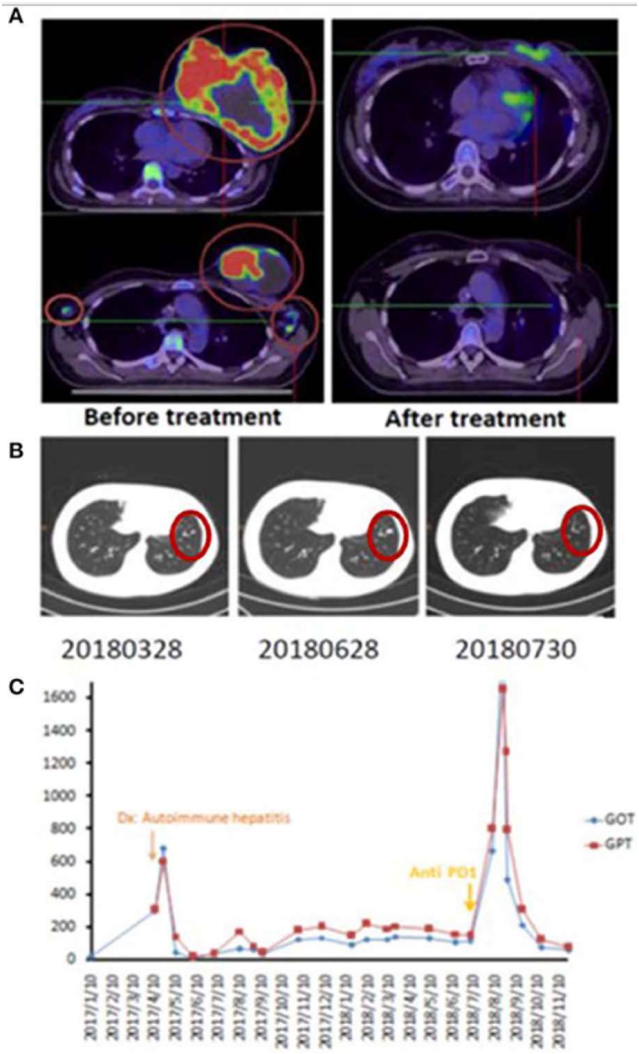

Figure 1. Representative patient (Case 1) with autoimmune mediated abscopal effects. (A) Locally advanced breast cancer with tumor abscopal effect on bilateral axillary and internal mammary lymph nodes. (B) Progressive lung metastatic lesions successfully salvaged with 2 cycles of low dose Opdivo®. (C) Flare up of autoimmune hepatitis by RT plus mEHT and ICP inhibitors.

Case 2

A 60-year-old female had right renal pelvis urothelial carcinoma diagnosed in October 2016. She underwent robotic right nephroureterectomy and bladder cuff excision, revealing a pT4N0 tumor treated with adjuvant tumor bed radiotherapy to 48 Gy in 24 fxs (completed in January 2017). In May 2017, she presented with a rapidly growing, painful, palpable abdominal mass. An abdominal CT scan showed multiple intra-abdominal masses and a right retroperitoneal mass attached to the right psoas muscle. The largest tumor was 4.5 cm. There was also a separate lower anterior abdominal wall mass and a liver segment 7 metastases. She received a second course of palliative RT targeting the symptomatic and dominant right lower quadrant mass and the lower abdominal wall mass, both treated to 40 Gy in 20 fxs, along with five weekly mEHT treatments. Concomitant carboplatin at 300 mg and gemcitabine at 600 mg were given for only two cycles and discontinued after pancytopenia developed. The abdominal pain resolved quickly, and she developed a mild fever with elevated CRP and pancytopenia in the 3rd week of treatment. A generalized itchy skin rash developed over the trunk in the 4th week of treatment. She was diagnosed with dermatitis herpetiformis and macrocytic anemia with positive anti-parietal cell antibody. The skin lesions were controlled with low-dose prednisolone (10 mg, once daily). A CT scan in August 2017 showed CR at the irradiated sites. Unexpectedly, an abscopal effect of the hepatic metastases was also identified (Figure 2) which was

unlikely to be from the systemic effect of only two cycles of low doses of carboplatin and gemcitabine. No further treatment was administered. A recent follow-up CT scan in May 2019, 2 years after palliative RT, showed persistent CR of all disease sites.

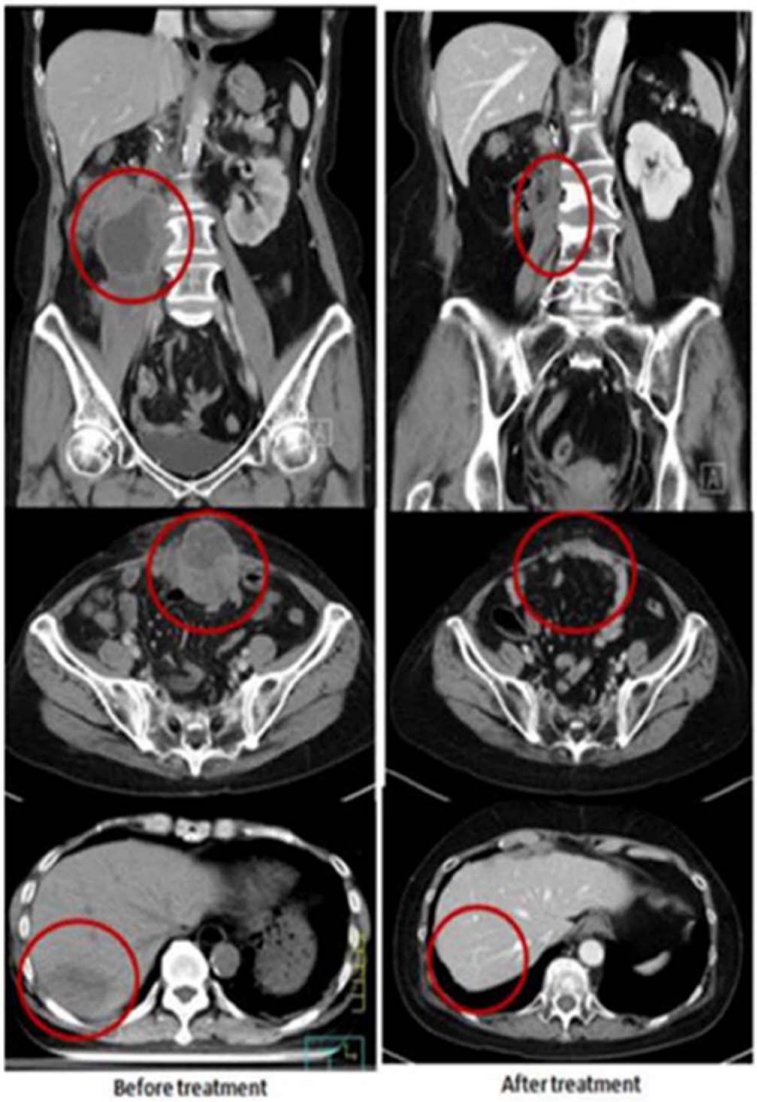

Figure 2. Representative patient (Case 2) with autoimmune mediated abscopal effects: metastatic urothelial carcinoma with abscopal tumor effect on liver metastases.

Case 3

This 69-year-old male patient had a biopsy-proven cholangiocarcinoma with multiple metastases diagnosed in August 2017. He began treatment with immunotherapy (Yervoy® at 50 mg for one dose only and Opdivo® at 60 mg every 2 weeks) for eight cycles, RT (45 Gy in 15 fxs to the liver, 30 Gy in 10 fxs to the scapula, L1 spine, and right pelvic bone), and weekly mEHT for 12 sessions starting from September 2017. In December 2017, he suffered from progressive muscle weakness with mild ptosis, lethargy, and difficulty in swallowing. He developed an aspiration pneumonia, requiring intubation and supportive management in the neurology intensive care unit. A positive acetylcholine receptor (AchR) antibody with electromyogram findings confirmed a new diagnosis of myasthenia gravis (MG). The patient gradually recovered after receiving plasmapheresis, steroids, and antibiotics. He did not receive any further anti-neoplastic therapy and was maintained on prednisolone, 5 mg once daily, for the subsequent 10 months. Follow-up imaging showed good PR at irradiated sites with measurable PR of the unirradiated L5 spine metastases. The CA 19-9 level peaked to 555 U/ml in

2018/3 and gradually dropped to 76.7 U/ml in 2019/6 (Figure 3) and he remained asymptomatic without any systemic treatment.

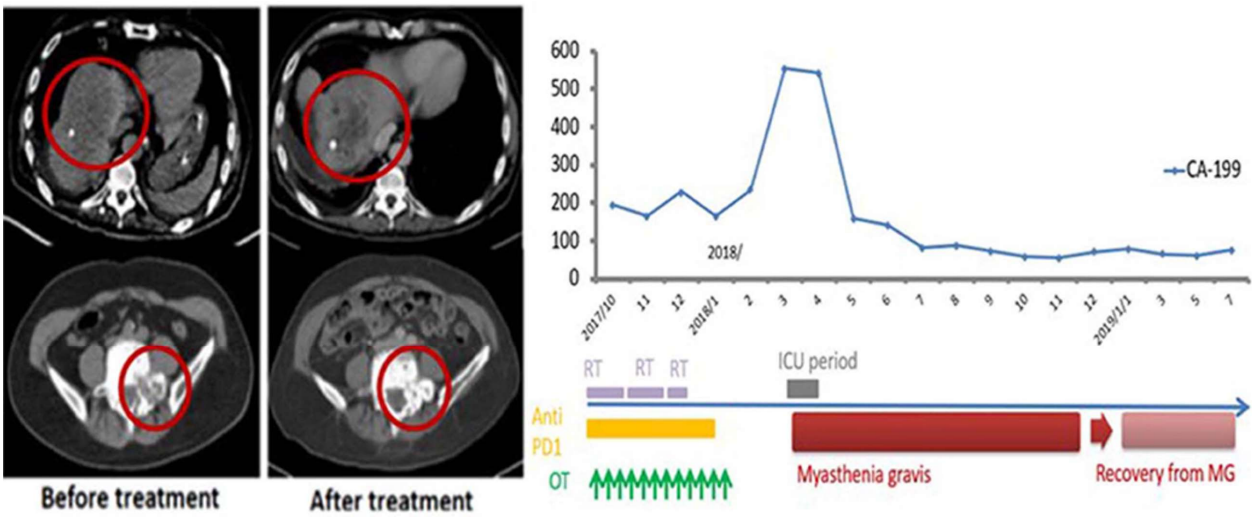

Figure 3. Representative patient (Case 3) with autoimmune mediated abscopal effects: metastatic cholangiocarcinoma with abscopal tumor effect on L5 bony metastases and change of CA-199 level.

Discussion

Although our patients were heterogeneous in terms of histology, lesion numbers, and prior treatments, in general, they represented a relatively common pool of patients referred for palliative radiotherapy, i.e., relatively large, symptomatic disease, either heavily pretreated or having declined during other therapies. In that context, the 60.6% overall response rates of the locally treated (RT plus mEHT) lesions may suggest a synergistic or radiosensitizing effect. Unexpectedly, tumors larger than 500 ml, had an even better response rate. Intriguingly, three cases of autoimmunity occurred after treatment, which was associated with abscopal tumor response.

What possible mechanisms could be at play here? The combination of systemic autoimmune effects and tumor abscopal effects provoked by combined mEHT and RT from local treatment leads us to speculate the possibility of the clonal expansion of a subset of T cells targeting both tumor antigens and shared normal tissue epitopes. These patients required steroids for managing their autoimmune reactions, without loss of tumor control. mEHT induces tumor cytotoxicity through a combination of localized thermal effects, and the temperature independent signal-excitation effect for DAMP release (12, 30). HSP-associated DAMP could facilitate immunogenicity, especially in the context of concomitant RT and possible combination with immune checkpoint inhibitors. The addition of ICP inhibitors after concomitant chemoradiotherapy (CCRT) in stage III lung cancer patients, improves both progression-free and overall survival rates relative to any other consolidative approach, suggesting the possibility that localized therapy creates a milieu for ICPs to have more durable effects (31, 32).

Are the local and abscopal responses reported herein, especially their depth and durability, expected and routine? Patients in this study were generally at such an advanced stage of their disease, that first, the expected response rates would be rather low, and second, durability would be very uncommon. This leads us to hypothesize that our clinical observations would require the development of unleashed anti-tumor autoimmunity, possibly from combinatorial mEHT and RT. In the three cases with autoimmune toxicity, Case 1 was treated with RT and mEHT only; Case 2 received only two cycles of reduced dose concomitant chemotherapy and Case 3 had immunotherapy with

RT. It would be very unlikely that the abscopal liver metastasis response in Case 2 was a chemotherapy effect. Whether the remote bony metastases response in Case 3 qualified as a pure "abscopal effect" is debatable. Nevertheless, the autoimmune reactions in the three cases after local treatment were quite clear. Immune response through in-situ vaccination might be amplified by the addition of ICP inhibitors as the third case described or might yield a deeper response as the second case described. Gauci et el. recently reported that in order to prolong survival, a CR or PR within 3 months after treatment was mandatory with anti-PD-(L)1 monotherapy for multiple cancer types (33).

Larger tumors had better responses to combined RT and mEHT treatment, which is counterintuitive. Explanations for this include the possibility that large tumors, especially those near the body surface under the electrode, absorb more energy from the RF current (34). For example, in an in vivo experiment, the use of a large 20 mm diameter electrode to deliver mEHT to 8 mm diameter size murine tumors resulted in impressive apoptosis, necrosis, and extracellular damage-associated molecular secretion patterns (12, 13), presumably because the entirety of the tumor was able to absorb energy effectively. Similarly, all eight breast cancers responded to this treatment. The radiation fractional dose used in our series is classic and typical for palliative radiotherapy, but atypical as far as several preclinical combinatorial immune checkpoint-radiation experiments recommend (for example 5–9 Gy per fraction, 3–5 fractions). Despite the use of lower fractional doses, the responses observed herein are robust. This could reflect the combinatorial use of mEHT. However, it is also worth considering that other clinical reports, such as the one by Chandra et al., demonstrated that radiation fraction size <3 Gy was the only parameter identified to be associated with favorable index lesion response in a cohort of melanoma patients treated with immune checkpoint inhibitors and radiotherapy (20).

As the use of immunotherapy becomes more popular, irAE is emerging as an issue (35). irAEs from ICP inhibitors are generally regarded as a "toxicity," however, a number of reports are beginning to appear in the literature claiming that patients with higher irAEs may have a higher response rate (36, 37). In addition, patients with irAE have longer treatment durations and more time to develop autoimmune toxicities (35). Clearly, immunotoxicity and autoimmunity is a balancing act. In our study, three out of 33 patients (9.1%) had induced autoimmune reactions from RT + mEHT. They all had a profound abscopal effect (>90% shrinkage of non-irradiated tumor, lasting for more than 12 months) without any substantial systemic targeted, cytotoxic, or ICP inhibitor therapy when autoimmune toxicities were noted. Most abscopal effects reported in the literature are neither "deep" (i.e., >90% tumor reduction), nor durable. For example, in the series by Golden et al. (23), only two of 41 patients (4.9%) had a dramatic abscopal response according to the criteria of >90% tumor reduction. Therefore, we argue that the effective immunity may be coupled to autoimmunity.

This case series of combining mEHT and RT for palliative purposes demonstrated unexpected autoimmune toxicities along with dramatic and sustained tumor regression. Despite being interesting and inspiring, these results must be interpreted with great caution and at best provide initial observations for hypothesis-generation, as there are considerable limitations given the retrospective, single institution analysis, with limited patient numbers, and considerable heterogeneity. An official prospective trial combining immune check point inhibitors with RT and mEHT will be launched.

Data Availability Statement

All datasets generated for this study are included in the article/supplementary material.

Ethics Statement

The studies involving human participants were reviewed and approved by Institute Review Board of Shin Kong Wu Ho Su Memorial Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author Contributions

M-SC, MM, and K-HC: conception and design and writing review of the manuscript. K-LY, H-CL, Y-SW, H-LK, Y-CL, and K-HC: development of methodology. M-SC: acquisition of data and analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis). K-HC: study supervision. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Keywords: modulated electrohyperthermia, immunotherapy, radiotherapy, abscopal effect, immune-related adverse events

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A Randomized Phase II Trial of Best Supportive Care With or Without Hyperthermia and Vitamin C for Heavily Pretreated, Advanced, Refractory Non-Smell-Cell Lung Cancer

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A randomized phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer

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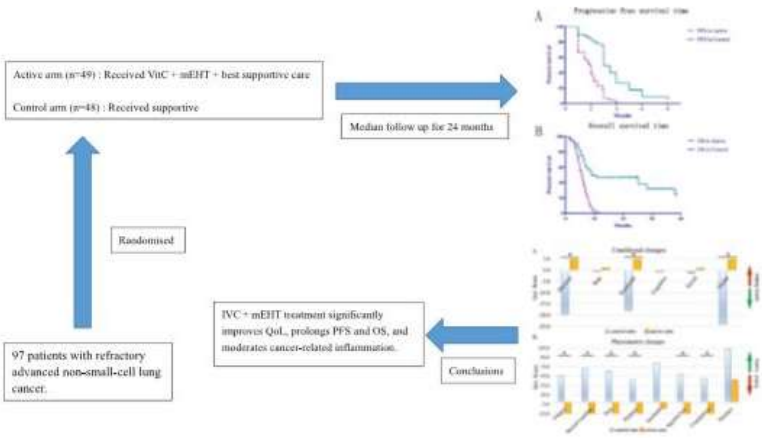
GRAPHICAL ABSTRACT



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ABSTRACT

Our previous study indicated that intravenous vitamin C (IVC) treatment concurrent with modulated electrohyperthermia (mEHT) was safe and improved the quality of life (QoL) of non-small-cell lung cancer (NSCLC) patients. The aim of this trial was to further verify the efficacy of the above combination therapy in previously treated patients with refractory advanced (stage IIIb or IV) NSCLC. A total of 97 patients were randomized to receive IVC and mEHT plus best supportive care (BSC) (n = 49 in the active arm,

Abbreviations: IVC, intravenous vitamin C; HT, hyperthermia; mEHT, modulated electrohyperthermia; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; QoL, quality of life; TKIs, tyrosine kinase inhibitors; BSC, best supportive care; AUC, area under the curve; PR, partial response; SD, stable disease; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; G6PD, glucose 6-phosphate dehydrogenase; DCR, disease control rate; CT, computed tomography; CR, complete response; QLQ-C30, Quality of Life Questionnaire; CI, confidence interval; EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma antigen; CA15-3, carbohydrate antigen 15-3; CYFRA21-1, cytokeratin-19 fragments; IL-6, interleukin- 6; CRP, C-reactive protein; TNF-α, Tumor Necrosis Factor-α.

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Remission rate

receiving 1 g/kg * d IVC concurrently with mEHT, three times a week for 25 treatments in total) or BSC alone (n = 48 in the control arm). After a median follow-up of 24 months, progression-free survival (PFS) and overall survival (OS) were significantly prolonged by combination therapy compared to BSC alone (PFS: 3 months vs 1.85 months, P < 0.05; OS: 9.4 months vs 5.6 months, P < 0.05). QoL was significantly increased in the active arm despite the advanced stage of disease. The 3-month disease control rate after treatment was 42.9% in the active arm and 16.7% in the control arm (P < 0.05). Overall, IVC and mEHT may have the ability to improve the prognosis of patients with advanced NSCLC.

Introduction

Lung cancer is the most common cancer type and the leading cause of cancer mortality in China [1], accounting for 19.6% of all newly diagnosed cancer cases [2]. Nearly 85% of lung cancers are non-small-cell lung cancer (NSCLC), which has a 5-year survival rate of 17.1%. The majority of patients diagnosed with NSCLC are found to be at an advanced stage. The overall survival (OS) of patients who fail to respond to conventional anticancer therapies (chemotherapy, radiotherapy, targeted therapy, immunotherapy, etc.) remains unsatisfactory.

The application of vitamin C for malignant diseases has had a renaissance [3]. Studies [4,5] have found that high-dose intravenous pharmacological administration of vitamin C produces plasma concentrations 100–1000 times higher than those of healthy nutritional levels and up to 100-fold higher than the maximally tolerated oral intake [6]. Phase I clinical trials show its safety, high tolerability and relief from the side effects of chemotherapy [7,8]. Clinical trials indicated the potential efficacy of intravenous vitamin C (IVC), with improved performance status or prolonged disease progression/overall time in ovarian [9] and pancreatic cancers [10]. Its synergy with chemotherapy improves quality of life (QoL) [10].

High-dose vitamin C is also applied for lung cancer. It decreases cell proliferation in lung cancer cell lines [11], including mechanisms of cell cycle arrest [12] and apoptosis [13]. Clinical studies [9] suggested that a large dose of IVC can increase the efficacy or reduce the toxic side effects of chemotherapy when used in synergy with chemotherapy. Recently, Schoenfeld [14] presented a phase II study of advanced-stage NSCLC patients (n = 14) treated with IV carboplatin (area under the curve (AUC), 6; 4 cycles), IV paclitaxel (200 mg/m^2, 4 cycles), and IVC (75 g twice a week, four cycles). No grade 3 or 4 toxicities related to vitamin C were reported. Four out of the 14 patients showed a partial response (PR), 9 out of the 14 patients showed stable disease (SD), and one showed progressive disease (PD), which indicated the potential efficacy of IVC in NSCLC therapy.

Hyperthermia (HT) is a method of treating tumors at the lesion site, which is mainly divided into local, regional, and whole-body HT. It is a complementary cancer treatment, often used in association with chemotherapy or radiotherapy, increasing the efficacy and prolonging the survival time [15,16]. Takayuki et al [17] suggested that HT and radiotherapy exerted a synergistic effect in the treatment of NSCLC. Modulated electro-hyperthermia (mEHT) is a regional electromagnetic HT method. The major advantage of mEHT is the nano-range energy liberation, rather than overall heating of the target [18]. Due to its high efficacy [18] and the synergy of the electric field [19], the targeted cancer cells absorb the heat that raises the temperature 3 °C higher than the enviorment [20]. Studies have found that the antitumor mechanism of mEHT is as follows: inducing cell apoptosis, improving tumor perfusion, inhibiting tumor angiogenesis and resolving tumor hypoxia [18,20–23]. Clinical data show that mEHT has long been used in clinical practice for various malignant diseases, and has clinical results for NSCLC [24–26]. mEHT can be used alone or in combination with radiotherapy (RT), chemotherapy, and chemoradiotherapy, and a growing number of studies are exploring combinations of mEHT and other therapies [27–29]. In a retrospective study, 93 patients with advanced NSCLC (stage IIIB-IV) were divided into HT combined with chemotherapy and chemotherapy groups, and the results indicated that HT combined with chemotherapy might lead to the development of a better therapeutic strategy for advanced NSCLC patients with malignant pleural effusion and greatly reduce the toxic effects of chemotherapy on the incidence of weakness and gastrointestinal adverse reactions in advanced NSCLC patients [30]. A multi-institutional prospective randomized trial observed that RT + HT improved local PFS in the treatment of locally advanced NSCLC [31].

In our previous phase I clinical study [32], we found that IVC with simultaneous mEHT is safe and well tolerated, and concomitant application significantly increases the plasma vitamin C level. The average scores for the functioning scale increased continuously, and the average values for symptoms decreased gradually, which indicates that QoL is improved when patients receive the above treatments.

Therefore, we conducted a randomized phase II trial to evaluate the effect of best supportive care (BSC) with or without IVC combined with simultaneous mEHT on tumor response, progression-free survival (PFS) and OS in previously treated patients with refractory advanced (stage IIIb or IV) NSCLC. Herein, we present the results of this trial.

Materials and methods

Patient recruitment

Eligible patients were adults (≥18 years ≤70 years) who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; who had a histologically proven diagnosis of primary NSCLC, stage IIIb or IV; who were not curable with surgery or showed radiographically confirmed PD during previous radiotherapy and/or four to six cycles of platinum-based chemotherapy (mostly cisplatin/carboplatin in combination with vinblastine, etoposide, or paclitaxel); who had failed to respond to targeted therapy or immunotherapy or were intolerant of their latest anticancer therapy regimen; and who showed at least one measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Table 1).

Patients were excluded if they showed G6PD deficiency or a history of oxalosis by urinalysis; were receiving anticancer therapies; were diagnosed with a comorbid condition that would affect survival, such as end-stage congestive heart failure, unstable angina or myocardial infarction within 6 weeks prior to the study; or had metallic implants or replacements in the treatment area or implanted electronic devices anywhere in the body.

Table 1
Patient baseline characteristics.

Characteristics	Active arm (n = 49)	Control arm (n = 48)
Age (years)		
Median	62	63
Range	42–72	43–72
Sex		
Male	38	37
Female	11	11
ECOG performance status		
Grade 0	25	26
Grade 1	12	11
Grade 2	12	11
Stage at study entry		
Stage IIIB	25	25
Stage IV	24	23
Pathology		
Squamous cell carcinoma	24	25
Adenocarcinoma	23	23
EGFR in Adenocarcinoma	2	0
EGFR in Adenocarcinoma		
EGFR(−)	13	6
EGFR(+)	10	17
Smoking status		
Current	3	4
Prior	36	33
Never	10	11
Unknown	0	0
Reason for failure of last anticancer therapy		
Refractory	45	43
Intolerant	4	5

ECOG: Eastern Cooperative Oncology Group.

All patients provided written informed consent. *The study was approved by the Ethics Committee of the Clifford Hospital affiliated with Jinan University. All patients provided written informed consent according to Good Clinical Practice (GCP) and national regulations [No: 2/2015-10].*

Study design and treatment

The study was a single-center, Phase II, randomized clinical trial. Trial Registration: ClinicalTrials.gov, NCT02655913; registration date, 7th Jan 2016. The date of enrollment of the first and last participants in the trial was 17th Jan 2016 and 17th July 2017, respectively, and all participants were recruited by the Clifford Hospital affiliated with Jinan University.

Eligible patients were randomized to receive IVC + mEHT + BSC (active arm) or BSC alone (control arm) (Fig. 1). BSC included multidisciplinary care, BSC documentation, symptom assessment and symptom management [32]. In the active arm, patients received IVC 1 g/kg·d three times a week for 25 treatments in total. Each milliliter of vitamin C injection contained 3 g of sodium ascorbate and water for injection, with the pH adjusted to 6.5–8.0 with sodium bicarbonate. Vitamin C was infused for 120 min. We used the mEHT method for HT treatment with the EHY2000+ device. This impedance-coupled device works with an amplitude-modulated 13.56 MHz carrier frequency, and its principles and practice are described in our previous study [32]. The treatment regimen of mEHT was 60 min/session; the power of mEHT was gradually increased from 135 W to 150 W depending on the patient's actual tolerance. The applicator used was 7.1 dm^2. The applied energy range in one session was between 486 kJ and 540 kJ. The patients were placed lying in the prone position, and the treatment covered the complete lung (30 cm diameter circle). The temperature of the treatment area was in the range of 40–42 °C, calculated indirectly by the treatment device. BSC focuses on helping patients obtain relief from symptoms such as nausea, pain, fatigue or shortness of breath.

The primary endpoint of this study was OS assessed by an independent investigator. Secondary endpoints included PFS, the 3-month disease control rate (DCR) that was defined as the proportion of patients with a complete response (CR) or PR or SD, QoL, and the association between biomarkers and treatment outcome.

Randomization and masking

We used a computer-generated random sequence to allocate patients (nonmasked) to BSC (control arm) or IVC + mEHT + BSC (active arm). The minimization method was used for randomization. When a new subject was added, the unevenness of the distribution of influencing factors in each group was calculated, and then the group of the subject was determined with different probabilities to ensure that the unevenness of the distribution of influencing factors was minimized. Patients were stratified by histology (adenocarcinoma or squamous cell carcinoma), ECOG performance status (ECOG score 0, 1, or 2), Epithelial growth factor receptor (EGFR) mutation in adenocarcinoma, medical records of anticancer therapies in the past 6 months, and stage of cancer.

Best supportive care

Since BSC was the control arm in our clinical trial, we designed a BSC program based on the recommendations from Zafar [33]. Patients from the BSC arm received appropriate treatments judged by the team including nurses, physicians, psychologist, and dietitians. Therapeutic measures included antibiotics, analgesic drugs, and dietetic assistance according to actual situations of patients. All the symptoms, supportive or palliative care methods and results were documented. Symptoms were assessed at baseline and throughout the trial in person. The symptom assessment was followed up by telephone every two weeks. Clinical assessment was performed during each hospitalization. Tumor-control assessment was assessed by radiographic examination every three months. Assessment methods are detailed in the study assessments section below. Symptom management was based on the National Comprehensive Cancer Network (NCCN) guidelines.

Study assessments

Enhanced chest and abdomen CT scans, brain MRI and bone scans were carried out at baseline and every 4 weeks for the first 12 weeks from the start of the study. All scans were assessed by an independent central radiology review. Response measurements were carried out according to RECIST 1.1. PFS was defined as the time from the onset of the study until disease progression or death from any cause. Three-month DCR was measured 3 months after therapy and defined as the percentage of subjects with a CR, a PR or SD at 3 months relative to all randomly assigned patients. We categorized patients as nonresponding when they had PD; otherwise, patients were categorized as responding. OS was defined as the time from randomization to death due to any cause. Adverse events were recorded, and their severity was assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. To evaluate the maintenance of improvement in the QoL, the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) was used.

Statistical analysis

The statistical systems GraphPad Prism 6 and PASS 15 were used for modeling and analysis. The sample size was determined

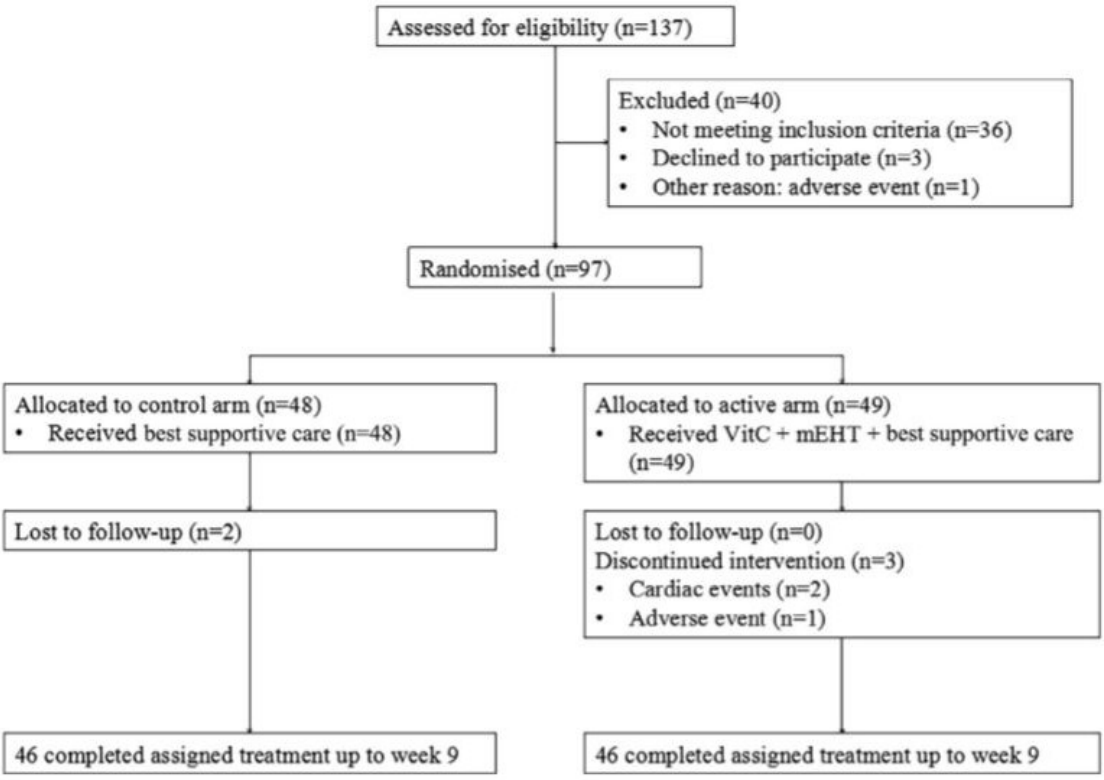

Fig. 1. Study design and patient disposition: Eligible patients were randomized to receive IVC + mEHT + best supportive care (active arm) or best supportive care alone (control arm).

to ensure that appropriate conclusions could be drawn with sufficient confidence. At least eighty-nine candidates were required, considering that a one-sided log-rank test with 45 active participants and 44 control participants achieves 85% power at a 0.05% significance level to detect a hazard ratio (HR) of 0.48 with a median survival time of 5.5 in the control arm for patients of Asian origin [34]. Survival estimates were analyzed using the log-rank test and the Kaplan–Meier method. Evaluation of short term response effects in two arms were examined by χ^2 test and T test. Comparisons of the study arms considering selected tumor markers and immune-associated factors were conducted using T test and Wilcoxon test. Descriptive statistics were used for treatment administration and safety.

Results

Patient characteristics

Between 2016 and 2017, 97 patients were randomly assigned to receive IVC + mEHT + BSC (n = 49) or BSC alone (n = 48) (Fig. 1). Demographics and baseline tumor characteristics were comparable between the groups (Table 1). The most common histologies were adenocarcinoma and squamous cell carcinoma. Two cases were adenosquamous carcinoma. EGFR exons 19 (n = 4) and 21 (n = 6) were mutated in the active arm.

Efficacy

The median follow-up time was 24 months. A total of five patients dropped out. Of them, two patients in the active arm experienced cardiac events; one patient suffered severe diarrhea. Two patients were lost to follow-up in the control arm. Efficacy analyses were performed in a modified intention-to-treat population of patients who did not receive other anticancer therapy before the cutoff date (May 1, 2019). Ultimately, based on the intent-to-treat principle, 97 patients were analyzed.

The log-rank test and Kaplan–Meier plots of OS and PFS showed highly significant differences ($P < 0.05$) between the active and control arms. The median OS was 9.4 months for the active arm and 5.6 months for the control arm [HR = 0.3268; 95% CI, 0.1582–0.4105; $P < 0.0001$]. The median PFS was 3.0 months for the active arm and 1.85 months for the control arm (HR = 0.3294; 95% CI, 0.1222–0.3166; $P < 0.0001$; Fig. 2). Neither OS nor PFS were affected by the pathological type of carcinoma ($P > 0.05$) (Table 2).

By using the RECIST 1.1 criteria, 5 of 49 (10.2%) subjects in the active arm had PR, while no PR was observed in the control arm; 16 of 49 (32.7%) subjects in the active arm and 8 of 48 (16.7%) subjects in the control arm had SD; and 28 of 49 (57.1%) subjects in the active arm and 40 of 48 (83.3%) subjects in the control arm had PD. No CR was observed in both two arms. The 3-month DCR was 42.9% in the treatment arm and 16.7% in the control arm (odds, 95% CI, $P = 0.0073$) (Table 3).

There were no significant differences in 3-month DCR, PFS or OS between adenocarcinoma and squamous cell carcinoma (Table 2) or between EGFR(+) and EGFR(−) subjects (Table 4).

None of the patients received further chemotherapy, radiotherapy, targeted therapy or immune therapy. However, in the active arm, four patients received a total of 50 follow-up IVC + mEHT treatments, and three patients received a total of 25 follow-up treatments (once a week).

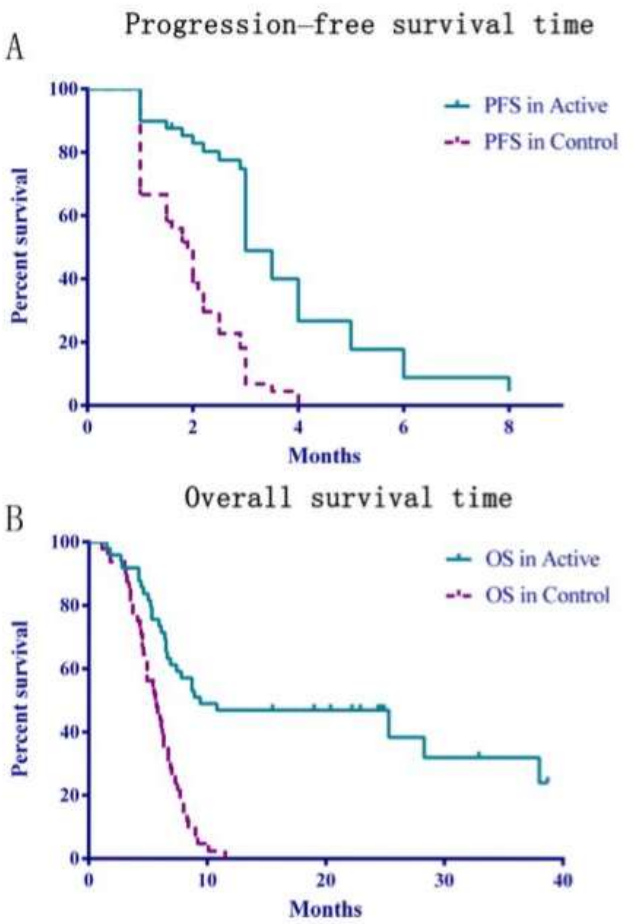

Fig. 2. Progression-free survival time (A) and overall survival time (B): Kaplan–Meier plots for progression-free and overall survival. A. The log-rank test for PFS for the two comparisons: active arm vs control arm [HR = 0.3294; 95% CI, 0.1222–0.3166; $P < 0.0001$]. B. The log-rank test for OS for the two comparisons: active arm vs control arm [HR = 0.3268; 95% CI, 0.1582–0.4105; $P < 0.0001$].

Table 2
Short-term response effects of squamous cell carcinoma and adenocarcinoma patients in the active arm.

Parameters	Squamous cell carcinoma (n = 24)	Adenocarcinoma (n = 23)	*P* value*
3-Month Response			
PR	3	4	0.563
SD	9	5	
PD	12	14	
3-Month DCR (PR + SD)	12	9	0.561
PFS (Median)	3 (months)	2.9 (months)	0.293
OS (Median)	12.45 (months)	10.8 (months)	0.616

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.
* Response effects of squamous cell carcinoma and adenocarcinoma patients were examined by χ^2 test and *T* test; $P < 0$ 0.05 indicates statistically significant difference.

Adverse effects and toxicity

The overall adverse effects of IVC and mEHT were marginal. Thirst was the major symptom during all of the treatments. Adverse effects were measured in 22/49 (44.9%) of subjects in the active arm. Symptoms disappeared when the treatments ended, except for one patient who experienced severe diarrhea (Table S1). This patient was withdrawn from the study at the stage when he ended the second combined treatment. Acute toxicity was not observed in other patients at any stage of treatment. No significant differences were registered in full blood count or biochemical and hematologic profiles before and after the treatment.

Table 3
Evaluation of short-term response effects in the active arm and control arm.

Parameters	Active arm (n = 49)	Control arm (n = 48)	*P* value*
Number of deaths (%)	30 (61.2)	46 (95.8)	<0.001
3-Month Response			
PR (%)	5 (10.2)	0 (0)	0.004
SD (%)	16 (32.7)	8 (16.7)	
PD (%)	28 (57.1)	40 (83.3)	
3-Month DCR (PR + SD) (%)	21 (42.9)	8 (16.7)	0.0073

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate.
* Response effects in the the active arm and control arm were examined by χ^2 test and *T* test; $P < 0$ 0.05 indicates statistically significant difference.

Quality of life

The QLQ-C30 scores were recorded over the full cycle of the study. The average scores for the functioning scales increased continuously, so QoL improved (Table 5).

In comparison, the differences in physical, emotional and global improvement after 9 weeks of therapy between the control and the active arms were significant. The psychometric parameters (symptoms) decreased gradually in the active arm of the study, despite the advanced NSCLC and the short (nine week) period of study. The symptoms in the control arm became stronger with time. Fatigue, nausea, pain, dyspnea, appetite loss and constipation were decreased significantly between the groups post treatment (negatively, corresponding to a decrease in symptoms). Note that no significant difference between the groups prior to treatment was observed.

Biomarker analysis

No significant differences in tumor markers, such as CEA, SCC, CA15-3, and CYFRA21-1, were observed before and after treatment or between the treatment and control arms (Table S2).

Inflammation markers

The statistical evaluation shows some significant changes in inflammatory immune factors. The complete comparison of the arms to each other shows more significance than the changes in the individual groups. IL-6 was not different in the two arms before the treatment ($P = 0.9413$) but differed significantly after therapy ($P = 0.0033$) and was lower in the active arm (Table 6). The difference originated from the active arm therapy ($P = 0.0046$), while the value in the control arm was nearly constant ($P = 0.1317$) (Table 6). The same was also observed for C-reactive protein (CRP); prior to therapy, the two arms were equal ($P = 0.7835$), but after therapy, they were significantly different ($P = 0.0205$) (Table 6). The value in the control arm was also unchanged ($P = 0.0729$). TNF-α did not significantly change between evaluations prior to and after treatment or between the arms of the study after therapy (Table 6).

Discussion

IVC and mEHT are widely used by integrative cancer practitioners for many years. To our knowledge, no studies have been

Table 4
Short-term response effects of EGFR(+) and EGFR(−) patients in the active arm.

EGFR in Adenocarcinoma	EGFR(+) (n = 10) 19 (+) (n = 4)	21 (+) (n = 6)	EGFR(−) n = 13	*P* value*
3-Month Response				
PR	3	0	0	0.100
SD	1	2	3	
PD	0	4	10	
3-Month DCR (PR + SD)	6		3	0.072
PFS (Median)	3 (months)		2.9 (months)	0.805
OS (Median)	21.8 (months)		7.8 (months)	0.253

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.
* Response effects of EGFR(+) and EGFR(-) patients in the active arm were examined by χ^2 test and *T* test; $P < 0\ 0.05$ indicates statistically significant difference.

Table 5
Function subscale and psychometric parameters.

Parameters	Prior treatment	Post treatment	*P* value*	*P* value (Active vs Control)#	
	Mean ± SD	Mean ± SD	Prior vs Post	Prior	Post
Physical					
Active arm	77.69 ± 16.70	85.71 ± 15.39	<0.0001	0.0533	<0.0001
Control arm	74.44 ± 13.21	59.93 ± 15.35	<0.0001		
Role					
Active arm	72.79 ± 24.70	73.54 ± 24.31	0.5000	0.8119	0.6919
Control arm	71.67 ± 23.43	71.39 ± 23.81	>0.9999		
Emotional					
Active arm	84.01 ± 20.33	88.61 ± 15.75	0.2633	0.4408	<0.0001
Control arm	83.68 ± 17.36	68.86 ± 19.20	<0.0001		
Cognitive					
Active arm	85.03 ± 18.40	85.03 ± 19.02	>0.9999	0.1862	0.1026
Control arm	81.25 ± 18.07	80.55 ± 17.97	0.5000		
Social					
Active arm	77.89 ± 22.15	78.43 ± 21.07	0.7500	0.2452	0.3953
Control arm	82.99 ± 19.90	81.94 ± 19.70	0.5000		
Global					
Active arm	46.25 ± 20.85	74.76 ± 20.11	<0.0001	0.0635	<0.0001
Control arm	52.77 ± 22.12	40.49 ± 22.77	<0.0001		
Fatigue					
Active arm	46.48 ± 17.52	20.63 ± 18.14	<0.0001	0.0770	<0.0001
Control arm	39.93 ± 20.59	61.34 ± 25.32	<0.0001		
Nausea/vomiting					
Active arm	24.83 ± 22.08	11.56 ± 26.18	0.0008	0.1460	<0.0001
Control arm	18.63 ± 20.26	31.94 ± 28.94	0.0007		
Pain					
Active arm	31.18 ± 21.21	25.51 ± 27.45	0.0205	0.4413	<0.0001
Control arm	28.82 ± 20.84	47.45 ± 24.55	<0.0001		
Dyspnea					
Active arm	38.09 ± 23.57	27.21 ± 22.23	<0.0001	0.4542	<0.0001
Control arm	34.03 ± 23.31	50.23 ± 26.61	0.0003		
Insomnia					
Active arm	35.37 ± 37.52	30.61 ± 30.30	0.2781	0.2068	0.0772
Control arm	23.84 ± 26.43	43.75 ± 33.09	<0.0001		
Appetite loss					
Active arm	29.93 ± 24.76	10.20 ± 20.64	<0.0001	0.4090	<0.0001
Control arm	25.00 ± 24.31	39.58 ± 26.32	<0.0001		
Constipation					
Active arm	23.81 ± 26.35	4.761 ± 11.78	<0.0001	0.1395	<0.0001
Control arm	17.36 ± 27.50	26.16 ± 31.38	0.0097		
Diarrhea					
Active arm	8.843 ± 20.16	12.92 ± 24.36	0.3283	0.7753	0.3014
Control arm	7.870 ± 19.71	7.870 ± 19.71	0.0112		
Financial problems					
Active arm	40.14 ± 35.99	21.09 ± 20.06	<0.0001	0.7496	<0.0001
Control arm	38.19 ± 30.74	56.94 ± 27.47	<0.0001		

*# *T* test was used when data of the two group fit the normal distribution, and *Wilcoxon* test was used when data didn't conform to the normal distribution; $P < 0\ 0.05$ indicates statistically significant difference.

Table 6
Inflammation markers in the active arm and control arm.

	Prior treatment	Post treatment	*P* value*	*P* value (Active vs Control)#	
	Mean ± SD	Mean ± SD	Prior vs Post	Prior	Post
IL-6					
Active arm	9.962 ± 6.408	6.674 ± 4.536	0.0046	0.9413	0.0033
Control arm	10.03 ± 6.506	10.08 ± 6.436	0.1317		
CRP					
Active arm	24.42 ± 28.45	14.43 ± 24.70	0.0134	0.7835	0.0205
Control arm	24.99 ± 28.68	25.30 ± 29.21	0.0729		
TNF-α					
Active arm	10.68 ± 23.38	8.777 ± 7.771	0.4930	0.7180	0.6782
Control arm	8.827 ± 10.35	8.963 ± 10.34	0.1012		

*# *T* test was used when data of the two group fit the normal distribution, and *Wilcoxon* test was used when data didn't conform to the normal distribution; $P < 0.05$ indicates statistically significant difference.

reported on mEHT combined with high-dose vitamin C in the treatment of tumors. Our phase I clinical study demonstrated that mEHT significantly improved QoL of NSCLC patients with less side effects [32].

This study shows that PFS and OS in the active arm were significantly improved compared with those in the control arm. The overall 3-month DCR was 42.9% with combination therapy, which was significantly higher than that with BSC alone (16.7%), indicating that our active therapy of IVC + mEHT may be an option for advanced NSCLC patients.

The reasons why there is a significant survival benefit are unclear, and we suspect two possible explanations. The first possibility is that the concomitant application of mEHT with IVC significantly increases the plasma concentration of vitamin C compared to that in the sole or nonconcomitant application of the treatments, which was proven by our phase I clinical trial [32]. Previous studies [12,35] demonstrated that vitamin C in pharmacologic concentrations generated H_2O_2, which selectively affected cancer cell lines but not normal cells. The increased VitC level can generate a high concentration of H_2O_2, which can react with the increased labile iron pools in cancer cells to mediate Fenton chemistry and cause oxidative damage to cellular DNA, protein, and lipids, resulting in an energy crisis and cell death [14]. Saitoh et al found that vitamin C combined with HT inhibited the growth of Ehrlich ascites tumor (EAT) cells through G2/M arrest and apoptosis induction via H_2O_2 generation at lower vitamin C concentrations, but the same concentration of vitamin C alone didn't exert the carcinostatic effect [36]. The results show that the combination of vitamin C and HT can induce synergic carcinostatic effects. Conventional HT often induces massive necrosis, while mEHT may avoide this outcome by its highly-selective nanoscopic heating [19]. One study indicated that mEHT produced a much higher apoptosis rate by selectively depositing energy on the cell membrane, compared with conventional capacitive coupling hyperthermia [21]. We suspect that the concentration of VitC is significantly increased by mEHT, which is key to attacking cancer cells.

However, in the active arm, we did not find any differences in 3-month DCR, PFS or OS between adenocarcinoma and squamous cell carcinoma or between EGFR(+) and EGFR(-) subjects. The mechanisms need to be addressed, which may be due to the small sample size of each group after stratification.

The second possibility is that IVC + mEHT can modulate the cancer inflammatory microenvironment. The cytokine IL-6 is the bridge connecting cancer cells to the inflammatory environment [37]. Clinical studies have indicated that an increased concentration of IL-6 is strongly associated with increased tumor size and poor prognosis in patients sufering from NSCLC [38,39], so it may be a potential target in cancer therapy. Cancer inflammation is accompanied by angiogenesis and an inflammatory microenvironment, which is also an independent prognostic marker of poor clinical outcome in NSCLC patients [38,39]. Welc et al detected HT upregulated IL-6 level in an animal model [40]. While some studies indicated vitamin C treatment attenuated synthesis of IL-6 [41,42]. In this study, we found that IL-6 level significantly decreased after 25 treatments in the active arm, and was significantly lower than that in the control arm.

Marsik [43] indicated that candidates with an increased level of CRP have a 28-fold increase in cancer-related death risk. Our study showed that CRP level also significantly decreased after 25 treatments, compared with the control arm. This is similar to the result observed by Mikirova [44], who found that IVC can suppress inflammation, as indicated by reduced CRP levels.

Meanwhile IVC + mEHT could significantly increase the functional scales and significantly decrease the symptom scales, so that QoL improved in these advanced NSCLC patients. Only mild adverse symptoms, such as thirst, fatigue and diarrhea were seen in the active arm. Symptoms (except for one patient with diarrhea) disappeared when the treatments ended.

In addition, 7 patients in the active arm felt better when they finished 25 treatments, and they spontaneously came to our center to receive another 25 to 50 follow-up treatments (once a week). We noticed that 4 of them (2 received 25 follow-up treatments and 2 received 50 follow-up treatments) had a tendency of longer survival time (OS: 38, 38, 37, and 32 months) than other candidates.

Conclusion

Overall, IVC has been shown to be safe and can produce various beneficial effects in nearly all kinds of cancer patients alone and in combination with chemotherapies. To our knowledge, this is the first study to evaluate the efficacy of IVC + mEHT for previously treated patients with refractory advanced (stage IIIb or IV) NSCLC who received BSC treatment. In summary, IVC + mEHT is well tolerated, significantly improves QoL, prolongs PFS and OS, and moderates cancer-related inflammation, so it is a feasible treatment in advanced NSCLC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2020.03.004.

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Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) Method: An Update for the Practicing Oncologist

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Background: Modulated electro-hyperthermia (mEHT) is a variation of the conventional hyperthermia which selectively targets the malignant cell membranes in order to heat the malignant tissue and sensitize the tissue to oncology treatments. Although widely applied, the formulation of guidelines for the use thereof is still in progress for many tumors.

Aim: In this paper we review the literature on the effects of mEHT in cancer patients on local disease control and survival.

Methodology: Our review on data presents the collected experience with capacitive hyperthermia treatments with the EHY-2000+ device (OncoTherm Ltd., Germany). A literature search was conducted in Pubmed and articles were grouped and discussed according to: trial type, animal studies, *in vitro* studies, and reviews. Search results from Conference Abstracts; Trial Registries; Thesis and Dissertations and the Oncothermia Journal were included in the discussions.

Results: Modulated electro-hyperthermia is a safe form of hyperthermia which has shown to effectively sensitizes deep tumors, regardless of the thickness of the adipose layers. The technology has demonstrated equal benefits compared to other forms of hyperthermia for a variety of tumors. Given the effective heating ability to moderate temperatures, the improved tumor perfusion, and ability to increase drug absorption, mEHT is a safe and effective heating technology which can be easily applied to sensitize tumors which have demonstrated benefits with the addition of hyperthermia. Modulated electro-hyperthermia also appears to improve local control and survival rates and appears to induce an abscopal (systemic) response to ionizing radiation.

Conclusion: Based on clinical studies, the method mEHT is a feasible hyperthermia technology for oncological applications. Concomitant utilization of mEHT is supported by the preclinical and clinical data.

Introduction

Moderate hyperthermia in oncology refers to the process of heating a tumor to within a range of 39–42.5°C in order to sensitize the tumor to oncology treatments (1). Although hyperthermia has been investigated in oncology since the early 1900s (2) there are still gaps in the knowledge and application of hyperthermia in many settings and in the effects of hyperthermia.

One example is the role of temperature in the treatment planning. Although an increase in temperature to above 43°C has direct tumor killing effects (3, 4), there are potential risks associated with high temperatures, such as enhanced blood flow to the surrounding tissues which may potentially aid dissemination of the malignant cells (5–7), and restricted blood flow within the tumor (8), reducing drug delivery to the tumor. Furthermore the homogenous heating of a tumor to a specified temperature is challenging due to the highly inhomogeneous nature of the tumor resulting in a variation in temperatures within the tumor from 37°C to in excess of 43°C, depending on the presence and size of necrotic areas within the tumor (3).

Despite the unanswered questions, local hyperthermia has shown to significantly improve local disease control in a variety of tumors (9), and offers a valuable addition to the basket of treatments available to treat localized disease. Unfortunately the survival benefit is not always as significant as the local disease control with the addition of hyperthermia (10–14) and a reduction in metastatic (systemic) disease is also needed in order to improve survival rates. This could be achieved with the induction of a systemic response to the treatment. Datta et al. (9) discusses the immunomodulating effects of hyperthermia and the potential for hyperthermia to promote an abscopal effect when combined with ionizing radiation (9).

Modulated electro-hyperthermia (mEHT; trade name: oncothermia) is a relatively new method of hyperthermia proposed by Szasz et al. (15) which differs from conventional heating methods in that it focusses on the selective heating of the extracellular matrix and cell membranes in the malignant tissue (16, 17) rather than on the homogenous heating goal of conventional heating techniques (18). Technically, mEHT is a precious impedance matched the capacitive coupled device, its effects are summarized in Figure 1. This paper reviews the clinical literature on mEHT. To our knowledge this is the first paper to conduct a review of literature published in Pubmed, focussing on clinical publications with limited focus on "gray" literature.

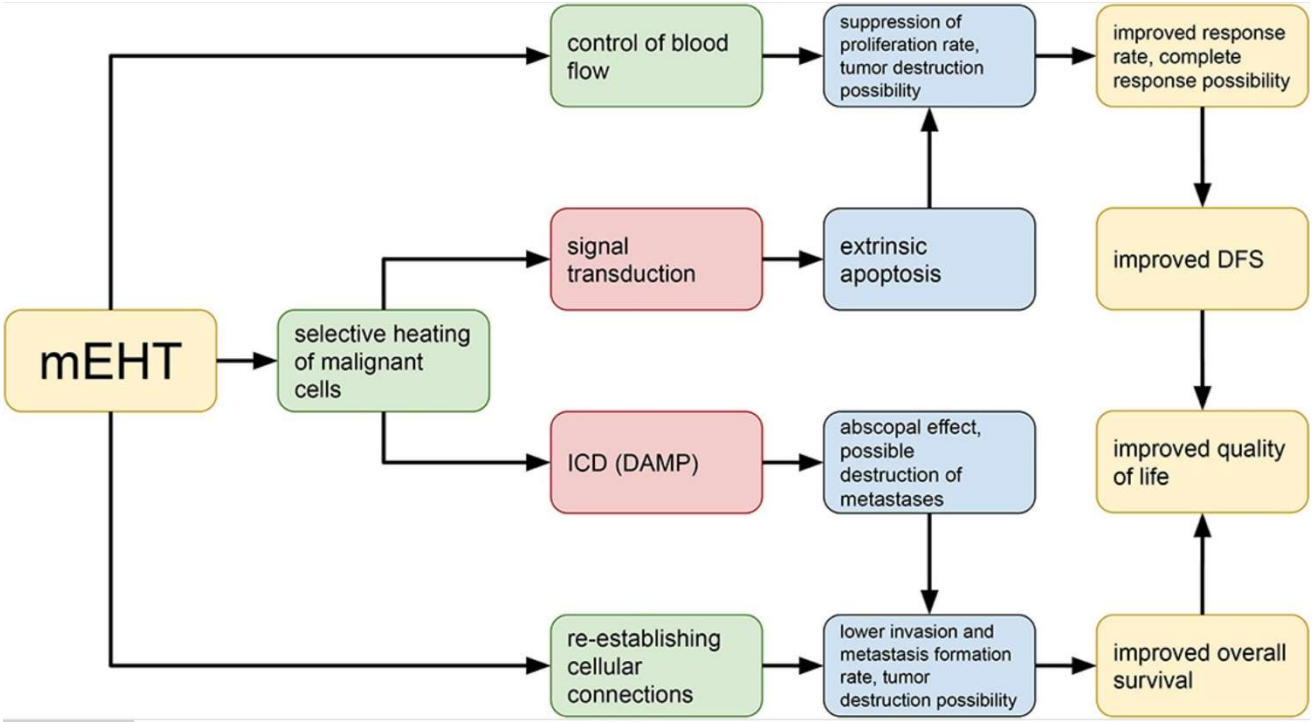

Figure 1. Basic principles of the pathobiological processes in the context of modulated electro-hyperthermia.

Methodology

A literature search was conducted in Pubmed using the string: "Cancer OR neoplasm OR tumor OR malignancies AND Oncothermia OR Oncotherm OR modulated electro-hyperthermia OR modulated electrohyperthermia" with truncated words included in the search. Articles were then classified as: Phase III randomized controlled trial (RCT); Non-randomized controlled trial; Phase I/II Trial; Animal studies; *in vitro* studies; "Gray" literature. The results were checked against a search for the same terms in the International Journal of Hyperthermia to make sure that all articles from the Journal were included in the search. "Gray" literature was included from Pubmed and from sources outside of the traditional commercial or academic channels and was further classified as: Expert reviews (from Pubmed); Case studies (from Pubmed); Conference Abstracts; Trial Registries; Thesis and Dissertations.

Results

The Pubmed search returned 46 articles, of which five were excluded as they did not involve the Oncotherm methods. Of the 42 eligible articles, six were from the International Journal of Hyperthermia and all articles on the Oncotherm method in International Journal of Hyperthermia appeared in the Pubmed search. Table 1 summarizes and categorizes the literature reviewed.

Deleted—not relevant (from Pubmed)	$n = 5$
Phase III randomized controlled trial (RCT)	$n = 2$
Non-randomized controlled trial (from Pubmed)	$n = 1$
Phase I/II Trial (from Pubmed)	$n = 10$
Animal studies and *in vitro* studies (from Pubmed)	$n = 18$
"Gray" literature	
Expert reviews (from Pubmed)	$n = 7$
Case studies (from Pubmed)	$n = 3$

Table 1. Summary of papers returned from the search string.

A search in ClinicalTrials.gov returned four trials registered and currently underway investigating the Oncotherm method

1. Multicenter RCT of the Clinical Effectiveness of Oncothermia With Chemotherapy (Folfirinox or Gemcitabine) in Metastatic Pancreatic Cancer Patients (Seoul National University Bundang Hospital, Republic of Korea); ID: NCT02862015.

2. A Trial of Weekly Paclitaxel with Oncothermia and Weekly cisplatin With Oncothermia in Patients With Recurrent or Persistent Ovarian Cancer (Seoul National University Bundang Hospital, Republic of Korea); ID: NCT02344095.

3. Effect of Oncothermia on Improvement of Quality of Life in Unresectable Pancreatic Cancer Patients (Seoul National University Bundang Hospital, Republic of Korea); ID: NCT02150135.

4. Modulated Electro-Hyperthermia Plus Chemo-radiation for Locally Advanced Cervical Cancer Patients in South Africa (Charlotte Maxeke Johannesburg Academic Hospital, South Africa); ID: NCT03332069.

There is a substantial amount of information available in the form of conference papers, books and expert reviews. Seven reviews on mEHT are available in Pubmed, primarily addressing the theory, biophysics and preclinical work on mEHT and containing references to conference papers, books and other references not addressed in this paper. As this information is discussed in detail in other papers, it is not addressed in this report.

Hegyi et al. (19) provides a detailed description of the goals and benefits of mild heating, effects of hyperthermia and the theory of mEHT. Another paper by Hegyi et al. (19) describes the cellular effects of hyperthermia compared to Oncothermia. The authors propose that the lack of acceptance of hyperthermia was in part due to the controversial results seen in hyperthermia trials published at the time and conclude that mEHT can solve many of these challenges, such as decreased risks of dissemination, deep heating, and selective heating. At the time however, mEHT lacked the clinical data and data on long term outcomes needed to optimize the protocols and implementation of the treatment (19).

Szasz (20) reviewed the use of mEHT for lung cancer patients and found mEHT to be a safe treatment with the potential to increase survival benefits and quality of life (20). In a very detailed and thorough review, Roussakow (21) reported on the use of mEHT for the management of recurrent glioblastomas. The paper evaluated the economic effect of the use of mEHT in these patients and concluded that mEHT significantly improves survival of patients treated with dose-dense temozolomide (21/28 days regimen) while also demonstrating cost-effectiveness (21). Based on this review and publications by Wismeth et al. and Fiorentini et al. (22–24). Prieto and Linares propose further research on thermosensitive liposomes combined with mEHT to manage brain tumors (25).

The biophysics of mEHT is dealt with in detail by Fiorentini and Szasz (26). Modulated electro-hyperthermia combines the effects of electric fields and heating to damage the malignant tissue. The selection is based on the differences in the electrical properties between healthy and malignant tissue (26). According to conventional hyperthermia the dose is measured by the temperature achieved in 90% of the tumor. This requires monitoring by either intratumoural thermometers or MR-technology (18). However the dose of mEHT is not measured by the temperature achieved in the tumor, but rather by the energy deposited in the tumor required to induce the sensitizing and cell-killing effects (26). The mathematical models and dosing concepts are dealt with elsewhere in the literature (27–29). Andocs et al. (30) effectively summarized the evolution of mEHT from the preclinical setting to the clinical setting showing the advantages of the mEHT compared to classical heat treatments at the same temperatures (30).

Safety of mEHT

The safety of mEHT has been demonstrated as a monotherapy in women with relapsed or refractory ovarian cancer. The aim of the study was to confirm the maximum tolerated dose of mEHT. Nineteen participants were treated with mEHT twice a week for 3 weeks, starting at 110 W and increasing the power to 130 W. No dose-limiting toxicities were noted with mEHT administered to the peritoneal region (31). An Italian study has also demonstrated the safety and tolerability of mEHT applied to a variety of solid tumors (32).

The effects of mEHT on the pharmacokinetics of nefopam (33) and fentanyl (34) were investigated in two randomized cross-over studies. The results showed that mEHT administered to the abdomen increased the absorption of nefopam administered orally and this resulted in an increase in the blood concentration of nefopam (33). This suggests that mEHT treatments may be used to increase the absorption of chemotherapy drugs at the heated site. The increase in overall exposure to oral transmucosal fentanyl citrate administered with mEHT was not associated with any clinical implications and is therefore considered safe to be administered in combination with mEHT (34).

Tumors in the brain and central nervous system are difficult to heat without risking damage to the healthy tissue. Two phase I/II studies have been conducted on mEHT applied to brain tumors. Fiorentini et al. (22) demonstrated the safety of mEHT in eight glioblastoma multiforme patients, two anaplastic astrocytoma (grade III) patients and two anaplastic oligodendroglioma. All patients had been previously treated with temozolamide-based chemotherapy and radiotherapy. Modulated electro-hyperthermia was applied up to 150 W without dose-limiting toxicities. The authors reported one complete remission and two partial remissions, a median duration of response of 10 months (range 4–32) and a 1 year survival rate 25%.

Wismeth et al. (24) confirmed the safety of mEHT with chemotherapy in a prospective single-arm Phase I trial involving 15 participants with high grade gliomas treated two to five times a week with mEHT (dose escalation protocol) combined with alkylating chemotherapy (ACNU, nimustin; 90 mg/m2). Participants were treated until dose-limiting toxicities developed or disease progression developed. Toxicities associated with mEHT included local pain, increased focal neurological signs, and increased intracranial pressure requiring mannitol or corticosteroids to resolve symptoms, however no dose-limiting toxicities developed (24).

Gadaleta-Caldarola et al. (35) reported excellent safety results following the use of mEHT combined with sorafenib for hepatocellular carcinoma. The authors investigated the combination as sorafenib inhibits cellular proliferation and angiogenesis and hyperthermia inhibits angiogenesis by damaging endothelial cells and increasing the expression of PAI-1 in the endothelial cells (36). The induction of apoptosis by mEHT has also been established in preclinical work (37–39). Twenty-one participants with advanced hepatocellular carcinoma were enrolled and treated three times a week with mEHT

for 6 weeks combined with sorafenib 800 mg on alternating days, followed by a 2 week break. The results showed stable disease in 50% of participants, partial response in 5 and 45% with progressive disease. Treatment related toxicities were associated with sorafenib and not directly attributed to mEHT and the addition of mEHT was well-tolerated and did not increase the sorafenib-related toxicities (35).

The intravenous administration of high doses of ascorbic acid is popular in the complementary and alternative fields of medicine. Ou et al. (40) showed that mEHT is safe to combine with intravenous ascorbic acid in non-small cell lung cancer patients in China. The researchers found that peak concentration of ascorbic acid was increased in participants treated with mEHT concurrently with the administration of ascorbic acid. However no dose-limiting toxicities were noted (40).

Cervical Cancer

Hyperthermia has been investigated extensively for the treatment of cervical cancer patients (41). In patients who are unable to receive the prescribed dose of chemotherapy, hyperthermia can be combined with radiation (42) with similar outcomes to chemoradiotherapy (43). Two randomized controlled trials investigating mEHT appeared in the Pubmed search, both on cervical cancer.

Lee et al. (44) investigated the use of mEHT combined with platinum based chemotherapies compared to chemotherapy alone for locally recurrent or residual cervical cancer post-radiotherapy. The combined results from two prior Phase II trials investigating hyperthermia and platinum based chemotherapy for locally recurrent cervical cancer showed an overall response rate of 54% (45, 46). Franckena et al. (46) subsequently recommended that this combined treatment be applied as a standard treatment approach for cervical cancer patients with locally recurrent or residual disease within a previously irradiated area. In the study by Lee et al. (44), patients were randomized to receive chemotherapy (paclitaxel + cisplatin; paclitaxel + carboplatin; cisplatom + 5-fluorouracil; or cisplatin) with (n = 20) or without (n = 18) mEHT for local recurrent cervical cancer patients who had been previously irradiated. A total of 36 mEHT treatments were administered (three times per week) beginning at chemotherapy initiation. The overall response to treatment was significantly greater in the group of patients treated with mEHT + chemotherapy ($p = 0.0461$), and the difference remained significant at the evaluation conducted at the last follow-up visit ($p = 0.0218$) with a complete response of 15% in the chemotherapy group vs. 50% in the combined group (47).

Minnaar et al. (48) report on early results from their phase III RCT on the use of mEHT combined with chemoradiotherapy (CRT) for locally advanced cervical cancer (LACC) patients in South Africa. The study was the first to include HIV-positive patients in a hyperthermia trial and it was conducted in a resource-constrained setting. Participants were randomized to receive chemoradiotherapy (CRT) (cisplatin, external beam radiotherapy, and high dose rate brachytherapy) or CRT + mEHT (administered twice per week for an hour, immediately before external beam radiotherapy). At 6 months post-treatment, 101 participants were available for evaluation in each group. Six month local disease-free survival and 6 month local disease control were significantly higher in the mEHT Group (n = 39 [38.6%] and n = 40 [45.5%], respectively), than in the Control Group (n = 20 [19.8%]); $p = 0.003$ and n = 20 [24.1%]); $p = 0.003$). The authors reported that mEHT did not have any effect on the frequency of CRT-related early toxicities and the outcomes were not associated with the body mass index of the patients, suggesting that therapeutic effects were seen even in participants with thicker layers of adipose tissue in the treatment field. In a comparison between the pre-treatment 18F-FDG PET/CT scans of participants with extra-pelvic nodes to the post-treatment scans of the same participants, the percentage of participants who showed a systemic response to treatment, with resolution of all metabolically active disease (including extra-pelvic nodes which were not in the treatment fields, pelvic nodes, and the primary tumor), was significantly higher in the mEHT Group: 24.1% (n = 13), vs. the Control Group: 5.6% (n = 3; $p = 0.007$) regardless of HIV status (48). These

results show mEHT is an effective hyperthermia technique producing results comparable to conventional hyperthermia, without unexpected toxicity. Preliminary results reported on 2 year disease-free survival showed a significantly higher disease-free survival in the mEHT group (49).

Lee et al. (44) showed that mEHT effectively improves the blood flow (measured by a Doppler ultrasound) to cervical tumors heated with mEHT in 20 patients. In their study the mean peri-tumor temperature was 36.7 ± 0.2 °C before heating and increased to 38.5 ± 0.8 °C at the end of heating for 60 min. This increase of roughly 2 °C is in line with the studies on other heating techniques applied to cervical tumors (50) and provides evidence of the radiosensitising effects for mEHT based on improved blood flow and subsequent improved oxygen in the tumoral environment.

Brain Tumors

In a non-randomized, multicenter, retrospective controlled trial, Fiorentini et al. (51) analyzed the effects of mEHT as a palliative option for the management of relapsed malignant glioblastoma (GBM) and astrocytoma (AST). One hundred and forty nine consecutive participants who had relapsed after surgery, adjuvant temozolomide-based chemotherapy, and radiotherapy, were enrolled (glioblastoma: n = 111; astrocytoma: n = 38). Participants were treated with mEHT (progressing from 40 to 150 W using a step-up heating protocol for 20 min progressing to 60 min) or best supportive care, as indicated. Twenty eight (25%) glioblastoma participants and 24 (63%) astrocytoma participants received mEHT three times a week for 8 weeks. Imaging studies were conducted every 3 months to assess response rates. At 3 months, an objective response (complete and partial response) in the AST participants treated with mEHT was significantly higher than in the AST participants treated with best supportive care (45 vs. 6%; $p < 0.005$). Progressive disease was observed in 4 (18%) of the AST participants in the mEHT group compared to 9 (56%) participants in the best supportive care group. Glioblastoma participants in the mEHT group had a significantly higher overall positive response (complete and partial response and stable disease) at three months than the participants in the best supportive care group (54 vs. 19%; $p < 0.05$). The 5 year overall survival of AST participants in the mEHT group was 83%, compared to 25% in the best supportive care group and the GBM patients treated with mEHT had a 3.5% 5 year survival compared to a 1.2% 5 year survival in the best supportive care group. These results provide strong motivation for further investigations into the inclusion of mEHT in the palliative management of GBM and AST patients with relapsed disease (23).

Peritoneal Metastases

Chinese hospitals frequently apply traditional Chinese medicine (TCM) combined with conventional treatments for a variety of disorders, including cancer. In a randomized Phase II trial in China (ClinicalTrials.gov ID: NCT02638051), mEHT combined only with TCM (n = 130) was compared to intraperitoneal chemo-infusion (IPCP) with cisplatin and fluorouracil (n = 130) administered twice, for patients with peritoneal metastases and malignant ascites. The "Shi Pi" herbal decoction was used for TCM and mEHT was applied every second day for 4 weeks. The overall response rate was 77.69% (101/130) vs. 63.85% (73/130) in patients treated with mEHT and IPCP, respectively, ($p < 0.05$) while the mEHT group reported less toxicity.

Case Reports

Yeo (52) describes a case of a 75-year-old patient with stage IIIB non-small-cell lung cancer treated with radiotherapy and mEHT. The patient was not eligible for radical treatment and chemotherapy due to the age and performance status of the patient. Radiotherapy was administered in 36 fractions

(total 64.8Gy) and mEHT was administered twice per week immediately before radiation (total 12 sessions). No dose-limiting toxicities developed and mEHT was well-tolerated. The follow-up imaging studies showed complete tumor response and the patient was disease free at 18 months post-treatment (52). The concurrent administration of bevacizumab and mEHT in a patient with bone metastasis from non-small cell lung carcinoma resulted in disease stabilization and improved pain management (53). Lee et al. (54) reported on a patient treated with mEHT, thymosin-α1, and a herbal treatment for lung metastases from a Wilms tumor in a patient previously treated with radiotherapy and chemotherapy. Disease stabilization of the lung metastases was noted on post-treatment CT scans (54).

The above research facts are verified in the clinical applications showing various clinical results (Figure 2).

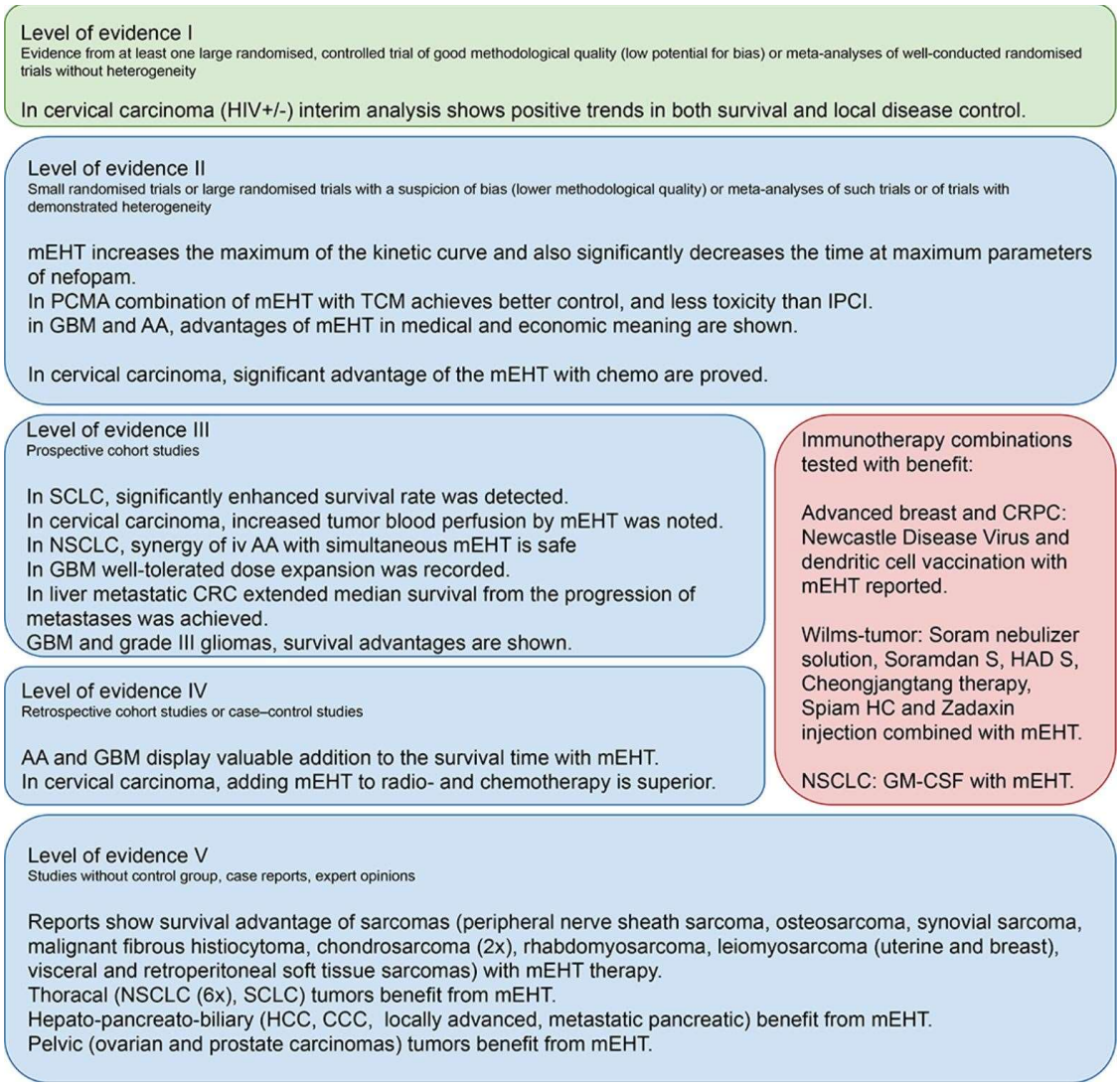

Figure 2. The verification and clinical evidence behind the modulated electro-hyperthermia clinical studies.

Conclusion

One of major challenges in hyperthermia is the safe treatment of tumors of the central nervous system and brain. Modulated electro-hyperthermia has shown safety in brain tumors (24) and efficacy for relapsed brain tumors as a monotherapy for palliative management (51). Capacitive heating is cited as being unable to effectively heat deep tumors (55, 56) however mEHT has

demonstrated safety and improved outcomes after the treatment of deep seated pelvic (cervical) tumors, even in obese patients (48). No dose limiting toxicities were noted in Phase I/II studies on peritoneal metastases in patients with recurrent disease from ovarian cancer, lung treatments (40) and treatments to the liver (35).

Modulated electro-hyperthermia is a safe form of hyperthermia which has demonstrated equal benefits compared to other forms of hyperthermia for a variety of tumors, including deep pelvic tumors. Minnaar et al. (48) showed that the body mass index of participants in their study was not associated with treatment outcomes, suggesting that mEHT effectively sensitizes deep tumors, regardless of the thickness of the adipose layers. Modulated electro-hyperthermia also appears to induce an abscopal (systemic) response to ionizing radiation (48) which is in line with the immunomodulating effects of mEHT described in the preclinical studies (9, 57). There does not appear to be an increased risk in disease dissemination and early results indicate improved disease free survival in patients treated with mEHT (23, 47, 48).

Given the ability of mEHT to heat tumors to within the moderate hyperthermia heating range [as demonstrated in a porcine model (58), other animal models (59–61). and human (44) studies], the improved perfusion, and ability to increase drug absorption, mEHT is a safe, and effective heating technology which can be easily applied to treat tumors which have demonstrated benefits with the addition of hyperthermia.

Author Contributions

AS and GPS: conception and design. AS, CM, GS, GPS, and MD: writing the manuscript. AS: construction of images.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia

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Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia

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ABSTRACT

Purpose: Preclinical studies and clinical observations suggest that amplitude modulation (AM) below 100 kHz may enhance the intratumoral power absorption of radiofrequency hyperthermia at 13.56 MHz; however, it remains unclear whether AM induces temperature-dependent effects.

Methods: We established tumor models assuming typical tumor architectures or cell suspensions to analyze the effects of additional power dissipation. The preconditions for demodulation at cell membranes *in situ* were outlined. The bioheat transfer equation was solved analytically for the selected models and the possibility of circumscribed temperature increases (point heating) with dependency on the specific absorption rate (SAR) peaks was estimated for centimeter down to nanometer scales.

Results: Very-low-frequency (VLF) AM radiofrequency can increase the SAR in the extracellular space or necrosis of tumors as compared to radiofrequencies alone. Such modulation-derived SAR peaks can induce higher temperatures (hot spots) in tumors with necrotic areas of millimeter to centimeter size. However, for lesions <1 cm, excessive (unrealistic) SAR > 1000, 10,000 and 10^{14} W/kg for diameters of ~5 mm, ~1 mm and ~10 nm (nanoheating), respectively, would be required to explain the cell kill observed in pre-clinical and clinical data, even with VLF modulation.

Conclusion: Our analysis suggests that VLF AM of radiofrequency hyperthermia for a theoretical tumor model cannot induce relevant temperature-dependent effects, as the associated temperature increases caused by the resultant SAR peaks are too small. Further investigation of possible non-temperature-dependent effects is recommended.

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Introduction

Radiofrequency (RF) hyperthermia using annular phased array (APA) techniques (70–140 MHz), capacitive systems (8–13.5 MHz) or local applicators (200–1000 MHz) has been validated for various tumor entities [1–5]. The basic physics, thermal dose concepts and associated planning are well understood [6–8]. Typically, only a specific absorption rate (SAR) of 10–20 W/kg is achieved in difficult-to-heat tumors; this can approach 60–100 W/kg under favorable conditions (i.e., for easy-to-heat tumors) [6]. The steady-state temperature increase θ [°C] in extended tumors is also influenced by the tumor perfusion w [ml/100 g/min] and can be estimated using a simple equation involving the SAR: $\theta = 1.5 \times SAR/w$. Therefore, the final intratumoral temperature is widely predetermined by anatomical and physiological determinants. In clinical practice, the most significant parameter as regards increased RF heating effectiveness is increasing the total power to the upper limit tolerated by the patient. Therefore, based on successful clinical trials (e.g., for cervical cancer), we can assume a typical total power >600 W for APA systems [6,9] and an even higher total power >800 W for capacitive techniques [10,11].

Recent clinical data [12] suggest that RF heating at 13.56 MHz in conjunction with amplitude modulation (AM) at very low frequencies *VLF* of the order of hertz to 10 kHz (called 'modulated electro hyperthermia [mEHT]') is effective, and permits use of much lower power levels [6,9–11]. A randomized trial [12] targeting locally advanced cervical cancer (standard radiochemotherapy with or without mEHT) revealed superiority of the experimental arm with respect to response/local control, with a total power of only 130 W. Further, the temperatures in the tumor were conceivably below those reported in [6,9–11]. Therefore, we hypothesize that additional non-temperature-dependent effects affected the results.

Moreover, in another recent study, mEHT with 40–150 W was applied as *mono-therapy* (without radiotherapy or chemotherapy) to target recurrent glioblastoma/astrocytoma III after standard treatment [13]. The researchers found objective remissions with volume reduction (i.e., complete/partial remissions) in one third of 50 patients, which is a surprisingly high response rate.

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An additional effect of VLF-modulation is also evidenced by preclinical studies on cell suspensions and experimental tumors. In those works, the researchers compared *water bath hyperthermia* [14–17] and *RF hyperthermia* [18] with a *modulated capacitive heating technique* (i.e., mEHT) using a carrier frequency ν of 13.56 MHz. Various experiments indicated stronger effects when mEHT was applied compared with water bath/infrared heating with the same temperature adjustments (typically 38 °C or 42 °C). Notably, Yang et al. [18] estimated a temperature difference of approximately 4 °C with comparable apoptotic cell rates for water bath heating and mEHT heating, which were performed at 46 and 42 °C, respectively.

Therefore, additional cell kill mechanisms may exist beyond the homogeneous temperature elevation (*via* water bath heating or infrared heating) achieved *via* VLF-modulation. Researchers often explain such data by assuming the occurrence of undetected temperature peaks (hot spots) during mEHT application. In such cases, the higher temperatures could primarily be due to the associated heterogeneous temperature distributions, which are inadequately sampled by conventional thermometry techniques.

This study explores the effects of mEHT application with regard to potential SAR peaks, which may cause hot spots. A theoretical approach is adopted, with the fundamental bioheat transfer equation (BHTE) being analytically solved for suitable models.

Methods

Model description

We adopted various tumor models based on typical tumor architectures or cell suspensions to analyze the effect of additional power dissipation. Figure 1 shows a single necrotic sphere of diameter *d* containing extracellular fluid (ECF) illuminated by constant *SAR* in an infinite medium with perfusion *w* and 0 *SAR*. Based on this model, we studied the temperature effects of high SAR peaks of extension *d*. The major advantage of this model is the existence of an analytical solution for the temperature distribution, which enables assessment down to microscopic dimensions (e.g., 10–100 μm).

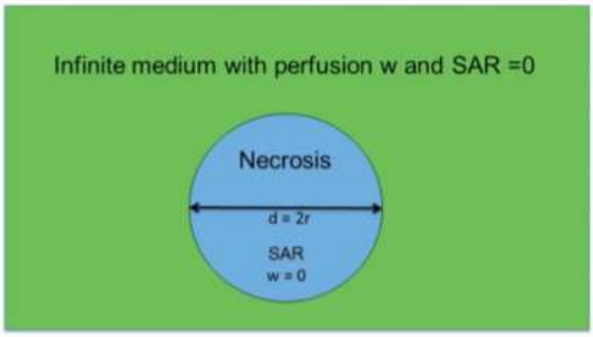

Figure 1. Simplified model of necrosis as sphere of diameter *d* with constant specific absorption rate (*SAR*) inside and perfusion $w = 0$. The sphere is embedded in an infinite medium with 0 *SAR* and arbitrary *w*.

Figure 2 shows a simplified three-dimensional model applicable to cell suspensions and some tumors (with typical microenvironments), consisting of cubical cell clusters of extension d_i (where index 'i' indicates 'intracellular'). These suspensions or tumor cell clusters are located in an extracellular medium with distance d_e (index 'e' indicates 'extracellular') between the cell clusters in all spatial directions *x*, *y*, *z*. The parameters $d_{i/e}$ may be selected to represent a variety of tumor architectures, from predominantly hydrated/necrotic ($d_e \gg d_i$) to solid ($d_e \ll d_i$) tumors. Clearly, the parameters $d_{i/e}$ can vary with position and indicate a local property of the tumor. The intra-/extracellular spaces V_{intra}/V_{extra} can be estimated from the relations

$$V_{intra} = N \times d_i^3 = L^3 \times [d_i/(d_i + d_e)]^3 \text{ and } V_{extra} = L^3 \times \{1 - [d_i/(d_i + d_e)]^3\}, \quad (1)$$

where $N = [L/(d_i + d_e)]^3$ indicates the number of cells or cell clusters in the tumor and *L* is the tumor size (Figure 2). The typical tumor microenvironment is characterized by high proportions of ECF and/or necrosis, which correlates with the common increased T2-intensity in magnetic resonance imaging of tumors. In the literature, we find typical data of >80% water content, i.e., <20% intracellular macromolecule content [19]. This yields >60% ECF, as illustrated by Figure 2. Note that a relationship of $d_i = 2 \times d_e$ yields 70% extracellular space according to Equation (1); this space is typically composed of 65% ECF and 5% plasma (in the vascular system) [20].

Conversely, in normal tissue, the total water content is 60% (intra-, extracellular, plasma) and, consequently, the macromolecule content is 40% [20]. This yields an extracellular space of 20%, as illustrated true-to-scale in Figure 3. That figure shows the typical structure of normal tissue (e.g., muscle or organ) containing functional units of parenchymal

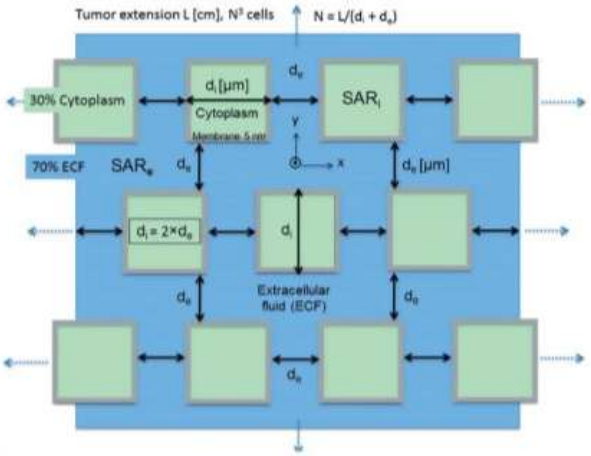

Figure 2. Simplified tumor model with cubical tumor cells or cell clusters of extension d_i ('i' for intracellular) in extracellular medium 'e' of width d_e. Assuming a tumor cube of edge length *L* [cm], we can determine the number N^3 of tumor cell clusters from d_i and d_e. The tumor is more solid and more hydrated for $d_i > d_e$ and $d_i < d_e$, respectively. The cell membrane has ~5-nm thickness. The cell cluster arrangement is continued in all directions. The figure illustrates a $d_i = 2 \times d_e$ relationship yielding 70% extracellular fluid (ECF, see text). This is a three-dimensional model with the coordinate origin and *x*/*y* axes plotted for analytical solution (Equations 7–9).

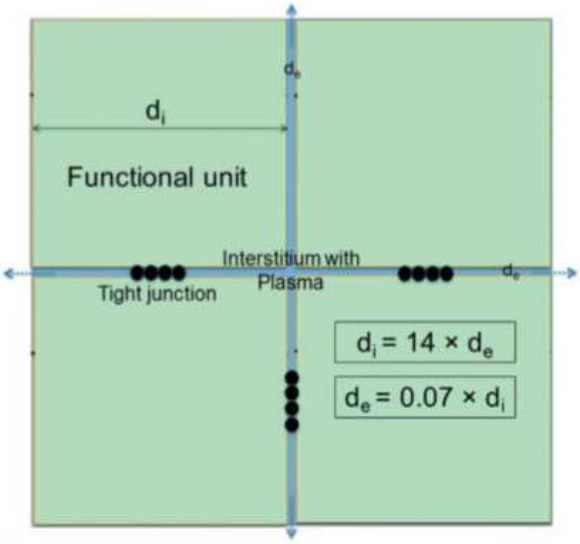

Figure 3. Simplified model of normal tissue such as muscle or liver. The extracellular space has a share of 20%, yielding this scale drawing (see text). Therefore, the functional units are considerably larger than the tumor cell cluster of Figure 2 and $d_e \ll d_i$. Because of the narrow interstitium of only a few micrometer, the membrane accessibility as regards electrical processes may be reduced. The membrane area is further decreased by the interconnections between the normal tissue cells (e.g., tight junctions), as sketched between the functional units.

cells arranged by connective tissue strands. An extracellular space proportion of 20% is achieved for $d_i \approx 14 \times d_e$, according to Equation (1). The cell-membrane interacting area in normal tissue is further diminished by the cell interconnections (as represented by the tight junctions in Figure 3).

Electrical constants

Table 1 summarizes the electrical properties of the intracellular and extracellular spaces used in the model of Figure 2, which are assumed as constant from direct current (DC) until 100 MHz [21,22]. The extracellular space is an electrolytic fluid similar to a 0.9%-NaCl solution with frequency-independent high electrical conductivity $\sigma_e = 1.2$ S/m. The lower electrical conductivity $\sigma_i = 0.3$ S/m of the cytoplasm is due to water bounded by proteins and may vary according to cell type [19]. For a cell membrane (index 'm') of 5–10 nm thickness, low dielectric values and extremely low electrical conductivities σ_m have been reported for frequencies <1 MHz with increasing σ_m above 1 MHz [22].

For biological tissue, the relative permittivity is known to be strongly dispersed (α- and β-dispersion in the kilohertz range and at some 100 kHz, respectively) as extensively studied in the past [19,23–25]; this is not reflected in Table 1, for the following reasons. First, these dispersions were found in normal tissue with much higher macromolecule and membrane concentrations than in tumors. Second, the relative permittivity is relatively unimportant for our low-frequency (<100 kHz) considerations, which are dominated by σ [19].

The electrical behavior at *VLF* is determined by the conductivity σ_e (Table 1), because the cell membrane acts as an isolator. Therefore, the different architectures found in tumors (Figure 2) compared with normal tissue (Figure 3) yield higher σ at audio frequencies. However, these notable differences may not be valid for every tumor and depend on the specific microscopic structure. Above 1 MHz, the membranes become increasingly transparent/conducting and the intracellular SAR SAR_i [W/kg] approaches 25% of the extracellular SAR SAR_e (derived from the σ_i/σ_e ratio given above). Therefore, in tumors, mean values σ_{TM} (where index 'TM' indicates 'tumor') of 0.6–0.8 S/m between σ_i and σ_e are reasonable assumptions for RF hyperthermia planning systems (10–500 MHz) [26,27].

The power per mass for alternating current (AC) electrical fields E is given by the relation SAR [W/kg] $= (\sigma/2\rho)E^2$, with the assumed simplification that the density $\rho = 1$ kg/l for all tissue. The typical mean SAR values achieved in tumors using clinical hyperthermia systems, either APAs or capacitive techniques, are 10–60 W/kg [6]; the corresponding E fields have amplitudes of 100–300 V/m (Table 1).

For $\nu \geq 1$ MHz, *dielectric power dissipation* is dominant; i.e., the rotational or vibrational energies of atoms and ions generated *via* interaction with $E(\nu)$. The SAR is split into different $SAR_{i/e}$.

For $\nu \leq 1$ MHz, however, *conductive power dissipation* becomes dominant. We assume that the cytoplasm region is surrounded by practically perfectly insulating cell membranes. Therefore, almost no current enters the cytoplasm and SAR_i becomes negligible. Thus, the power is deposited *via* ion currents in the widely connected extracellular space that characterizes many tumors.

Demodulation

VLF-related conductive power dissipation may be possible in tumors through application of VLF-AM for a *VLF* of some kHz and an RF ν of 13.56 MHz [28]. To cause VLF-currents in the tumor, this particular tumor tissue must act as a *demodulator*. In terms of an *equivalent circuit*, the tumor cell membranes operate like barrier-layer rectifiers (diodes) and form a capacitance C (~μF/cm^2), while the ECF and specific channels act as resistors (R ~100 Ω × [cm^2]), as illustrated in Figure 4. That diagram shows the basic circuitry of the earliest receiver known as the 'crystal radio receiver' (see Wikipedia). Demodulation is realized by rectification (where the cell membrane is analogous to a diode) in conjunction with smoothing (*via* C and R). The time constant RC must be between the cycle times of the carrier ($1/\nu$) and the modulation frequency ($1/VLF$) for a proper (distortion-free) demodulation [29]. We expect considerably a greater demodulation in the tumor, which is composed of widely connected and abundant ECF adjoining rectifying membranes. Because the other (preferably normal) tissue has no strong ability to demodulate, the AM carrier signal passes through without generation of VLF-currents. Thus, when both ν and *VLF* are appropriately selected, VLF-conduction may only occur in a limited volume of the exposed body region. This is particularly valid for tumors having suitable microenvironments.

Table 1. Compilation of physical constants and formulas used in main text [6,21–22]. For our purposes, the frequency range can be restricted to <100 MHz. The relaxation times depending on the spot size are given below (see Discussion).

$\kappa = 0.6$ W/m/°C	Thermal conductivity (tumor)
$\rho = 1.0$ kg/l	Density (water)
$c = 4000$ Ws/kg/°C	Heat capacitance (tumor)
$\sigma_e = 1.2$ S/m	Extracellular medium conductivity (DC – 100 MHz)
$\sigma_i = 0.3$ S/m	Cytoplasm conductivity (DC – 100 MHz)
$\sigma_m = 3 \times 10^{-7}$ S/m	Membrane conductivity (<1 MHz)
$c_m = \varepsilon_m/d = 0.9 \times 10^{-2}$ F/m^2	Membrane capacitance
$\cong 1$ μF/cm^2	$\varepsilon_m = 4.4 \times 10^{-11}$ As/Vm, $d = 5$ nm (membrane)
$\varepsilon_{r/e} = 72.5$	Extracellular medium relative permittivity (DC – 100 MHz)
$\varepsilon_{r/i} = 72.5$	Cytoplasm relative permittivity (DC – 100 MHz)
$\varepsilon_{r/m} = 5$	Membrane relative permittivity (<10 MHz)
$E = 100$–300 V/m	E-field for SAR = 10–60 W/kg
	E = 200 V/m for SAR = 25 W/kg
$\tau = d^2 \rho c/\kappa$	Relaxation time for hot spot of extension d
	$\tau = 10$ s for d = 1 mm
	$\tau = 10^{-1}$ s for d = 100 μm
	$\tau = 10^{-3}$ s for d = 10 μm
	$\tau = 10^{-9}$ s for d = 10 nm

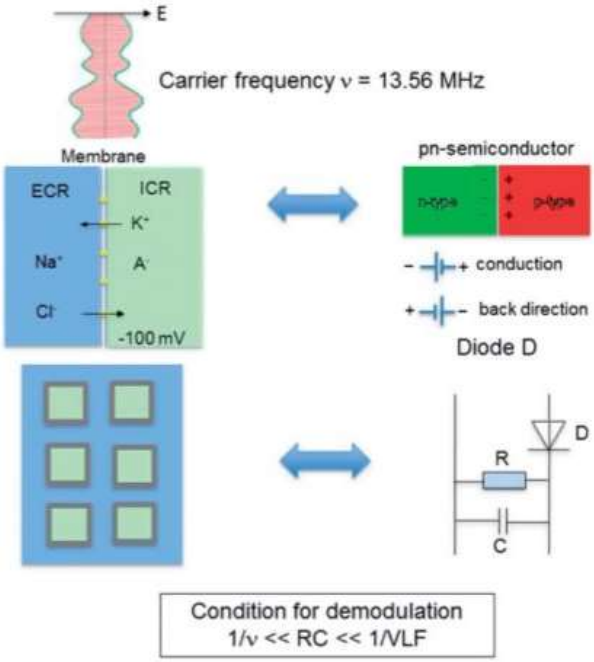

Figure 4. Equivalent circuit diagram of tumor, acting as demodulator of AM RF frequency at 13.56 MHz. The membranes (top left) are comparable to a rectifier diode (top right), because they have high permeability/conductivity for K^+ and Cl^- ions (forward direction) and are much less permeable for Na^+ and A^- (backward direction). The resistance R and capacitance C of the membranes or cell formations of the tumor determine the demodulation condition (see text). The electrical parameters can be derived utilizing the parameters of Table 1. The power absorption of the tumor may be increased by adjusting the carrier frequency ν or the modulation frequency spectrum to the specific tumor (bottom left) and its electrical attributes (bottom right).

In the case of a basic double-sideband (DSB) AM scheme (DSB-AM), ν is fully modulated by VLF frequencies with a modulation index $m = 1$. Then, the total power of the sidebands is equal to half the carrier power [29]. The power relationship between the carrier and sidebands can be modified in favor of the latter, e.g., by using a DSB reduced carrier (DSB-RC) transmission. Therefore, the sideband power can range from half the total RF power $P(\nu)$ for DSB-AM with $m = 1$ to a multiple of $P(\nu)$ for DSB-RC, and will increase the VFL-related power transfer in the tumor ECF. This may yield enhanced generation and absorption of VLF-currents. In consequence, the local SAR in the tumor ECF generated by VLF-demodulation and conduction, $SAR_{TM}(VLF)$, can be higher than the (mean) SAR in the tumor generated by the carrier frequency $SAR_{TM}(\nu)$ alone. We describe this effect by the following equation:

$$SAR_{TM}(VLF) = K \times SAR_{TM}(\nu) \quad (2)$$

In our calculations, we take $K = 1$–100 as an assumed power range in order to estimate the effect due to enhanced VLF-current conduction in tumors. A special modulating frequency that maximizes K may exist in the VLF-range, depending on the individual tumor architecture. Matching of the modulated power through proper selection of the modulating frequency spectrum is a possible strategy for increasing/maximizing K, which is in principle unknown for every new case [28].

Note that an increase of $SAR_{TM}(VLF)$ up to 100 W/kg in the ECF of a 100-ml tumor (~6 cm extension) requires a total power of only 10 W, which is a small portion of the total power from the amplifier. Furthermore, assumption of $K > 10$ (or even $K > 2$) in Equation (2) is probably unrealistic. However, such a hypothesis is tested to clarify whether temperature-dependent effects can occur as a consequence of exceedingly high SAR in a circumscribed necrosis with diameter d (Figure 1) or in a tumor ECF of width d_e (Figure 2).

BHTE formulation

On a microscopic level, the SAR distribution is heterogeneous and follows the rules outlined in the previous section. However, determination of the corresponding temperature increase θ is much less straightforward, because of the rapid heat redistribution that occurs at microscopic dimensions of size $d = 1$–10 nm according to the thermal equilibration relaxation time $\tau = d^2c/\kappa$, listed in Table 1 using the constants c, κ in Table 1.

The value of θ in the steady state is approximated by the well-known BHTE [30] with source term SAR and an omnidirectional w [ml/100 g/min]:

$$(\kappa/\rho)\nabla^2\theta + \rho_b c_b \times w \times \theta + SAR = 0, \quad (3)$$

using the constants κ, ρ(water), ρ_b(blood), c(water), c_b(blood) described in Table 1.

Results

The power deposition patterns (SAR) in Watts per kilogram can be estimated on a microscopic level for nanotherapy or various electromagnetic techniques. In the case of mEHT, we employ simple three-dimensional models and assume arbitrarily high SAR in the ECF, which is deposited by currents at low frequencies (Figures 1 and 2). Then, the temperature distribution can be evaluated utilizing numerical methods; however, this is a difficult task in the case of microscopic dimensions (down to nanometer scale). Therefore, in this study, we adopted an alternative approach and searched for *analytical solutions*, which are not restricted by physical dimensions, memory space, computing speed or numerical inaccuracies. We investigated whether undetected small, or even microscopic, hot spots (exposed to temperature increases >5–6 °C) can explain the data reported in Refs. [12–18].

In the following, we report deduction of the analytical solutions of the BHTE (Equation 3) for the models shown in Figures 1 and 2. The inserted physical constants are listed in Table 1.

Analytical solution for Figure 1 model

We formulated the BHTE in spherical coordinates:

$$\partial^2\theta/\partial r^2 + (2/r) \times \partial\theta/\partial r - (\rho_b \rho c_b/\kappa) \times w \times \theta = 0 \text{ for } r \geq 1/2d, \quad (4a)$$

$$\partial^2\theta/\partial r^2 + (2/r) \times \partial\theta/\partial r + (\rho/\kappa) \times SAR = 0 \text{ for } r \leq 1/2d. \quad (4b)$$

After straightforward calculation with $\theta_{in}(½\, d) = \theta_0$ and $\theta_{in}(0) = \theta_{max}$, we achieved (assigning the parameters of Table 1 and taking r in centimeter):

$$\theta_{out}(r \geq 1/2d) = \theta_0 \times (d/2r) \times \exp\left(-(0.1w)^{1/2}(r - 1/2d)\right), \quad (5a)$$

$$\theta_{in}(r \leq 1/2d) = \theta_{max} - 0.028 \times SAR \times r^2, \quad (5b)$$

where θ_{out}, θ_{in}, θ_0 and θ_{max} are the temperature elevations outside, inside, at the edge and at the center of the sphere, respectively. Note that θ_{max} is also the maximum temperature increase. Hence, the temperature elevation $\theta(r)$ exhibits an inverted parabola inside the sphere and an exponential decline outside.

Finally, employing the following boundary conditions at the edge ½d of the sphere:

$$\theta_{in}(1/2d) = \theta_{out}(1/2d) \text{ and } \partial\theta_{in}/\partial r(1/2d) = \partial\theta_{out}/\partial r(1/2d),$$

we obtained formulas allowing estimation of the temperature elevations θ_0 and θ_{max} [°C] for the sphere depending on d [cm], SAR [W/kg] and w [ml/100 g/min]:

$$\theta_0 = d^2 \times 0.014 \times SAR/\left(1 + 1/2d(0.1w)^{1/2}\right), \quad (6a)$$

$$\theta_{max} = \theta_0 + 0.007 \times SAR \times d^2, \quad (6b)$$

and for

$$w = 0 : \theta_{max} = 0.021 \times SAR \times d^2. \quad (6c)$$

Note that the induced temperature elevation increases (only) linearly with SAR, but has a fast quadratic decay with declining d.

Analytical solution for Figure 2 model

We formulated the BHTE in Cartesian coordinates of x, y and z:

$$\nabla^2\theta + (\rho/\kappa) \times SAR = 0. \quad (7)$$

The general solution is

$$\theta(x, y, z) = A(x^2 + y^2 + z^2) + B(x + y + z) + C. \quad (8)$$

By substituting (8) into (7), we obtained $A = -(\rho/6\ \kappa) \times SAR$ and, for reasons of symmetry, $B = 0$ ($\theta(-x, 0, 0) = \theta(+x, 0, 0)$). Defining the coordinate origin in the center of the extracellular space 'e' according to Figure 2, we assumed for every direction x, y, z the same $\theta(x, y, z)$ behavior. In the center of the aqueous space the temperature increase is maximal, $\theta_e(0,0,0) = \theta_{max}$. By considering ½$d_e$ in every direction x, y, z to the furthermost point at the cell membrane, we found the minimum temperature increase θ_{min}, i.e., $\theta_{min} = \theta_e(½d_e, ½d_e, ½d_e)$. Then, assuming $SAR_i = 0$, we obtained for the temperature difference $\Delta\theta$ [°C] (Figure 2):

$$\Delta\theta = \theta_{max} - \theta_{min} = (\rho/8\kappa) \times SAR_e \times d_e^2 = 0.021 \times SAR_e \times d_e^2, \quad (9)$$

where SAR is in Watts per kilogram; d_e is in centimeter, $\kappa = 0.006$ W/cm/°C and $\rho = 0.001$ kg/cm^3 (Table 1). Note that the predicted (additional) temperature increases θ_{max} or $\Delta\theta$, respectively, are equal for both models (Figure 2/Equation 9 versus Figure 1/Equation 6c).

We assumed a mean $SAR(\nu)$ at the tumor within the range of 10 to 60 W/kg (from difficult to easy to heat, respectively). Equation (2) predefines the additional power provided by the VLF-AM to the tumor stroma, either a necrosis with diameter d or tumor ECF of width d_e.

Equations (5) and (6) were used to evaluate the likelihood of 'point heating', i.e., the creation of circumscribed temperature elevations (hot spots) by high SAR peaks of limited size. Advantageously, for arbitrary values of SAR and d (i.e., for a heated sphere of diameter d), θ could be calculated and the actual temperature estimated by adding a systemic temperature of 37.5 °C. We quickly recognized that effective heating in small volumes of microscopic dimensions < millimeter scale is virtually impossible, if realistic SAR are assumed.

Figure 5 (top) illustrates that, in a sphere of 1-cm diameter, $SAR = 200$ W/kg is required for temperatures >41.5 °C. Further, if $SAR = 100$ W/kg is achieved (still challenging), the temperature elevation is only 39.6 °C. If we assume the occurrence of SAR peaks in volumes of 5 mm (Figure 5, bottom), excessive $SAR = 800$ W/kg is required in order to achieve a temperature >41.5 °C. Even $SAR = 400$ W/kg yields unsatisfactory temperatures of 39.6 °C. In summary, either unrealistically high SAR (> hundreds of Watts per kilogram) and/or large heated volumes (> centimeter scale) are necessary to achieve effective temperatures. In addition, according to the curves of Figure 5, the temperature increase scales

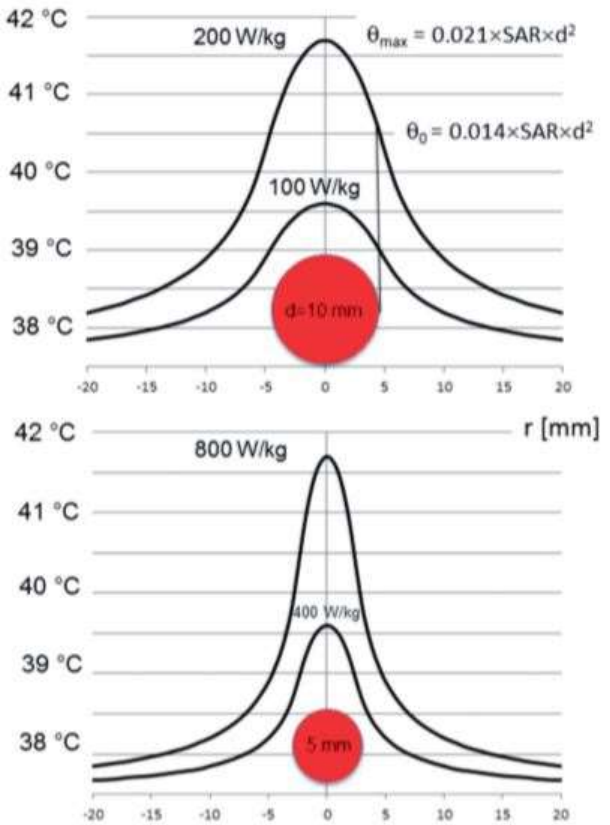

Figure 5. Temperature distributions for SAR peaks in spheres of 5-mm (bottom) or 10-mm (top) diameter, illustrating the possibility of 'point heating'. For lesions of ≤1 cm, extremely large SAR of hundreds of Watts per kilogram are required to obtain a relevant temperature >41 °C (still far from cytotoxic temperatures). On the other hand, temperature elevations of centimeter range around the lesion are measurable. Therefore, 'point heating' in the absence of bulk heating is physically impossible. The formula for the maximum temperature increase θ_{max} in the lesion center (Figure 1) or the ECF (Figure 2) is given together with the temperature increase θ_0 at the edge. The temperature at the ordinate is given by 37.5 °C+θ (using Equations 5a and 5b).

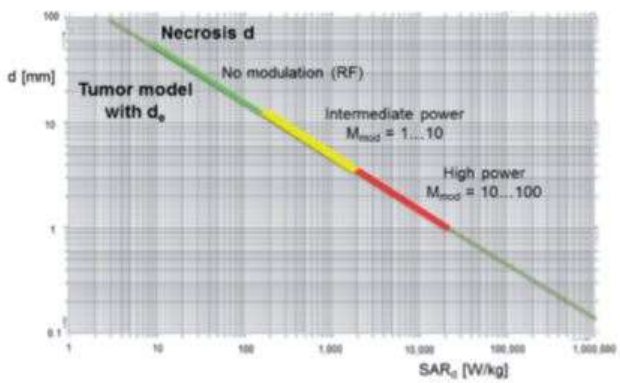

Figure 6. Diameters d of spherical hot spots (θ_{max} = 6 °C) versus required SAR peaks in sphere. Three colored ranges of hot spot development according to the degree of power enhancement K by VLF modulation are shown. For RF alone (K = 0), up to SAR = 100 W/kg, only necrotic/aqueous areas of centimeter size can be heated. For high power dissipation *via* VLF modulation (K = 100) above SAR = 10,000 W/kg, necrotic/aqueous areas down to millimeter d are effectively heated; however, necrotic/aqueous areas of microscopic dimensions (e.g., d of 100 µm) are still excluded. For areas of $d \sim 100$ µm, excessive (unrealistic) values of SAR > 1,000,000 W/kg are required. This general diagram is also valid for microscopic d from micrometer down to nanometer scales (nanoheating range), requiring SAR values of up to a quadrillion (Equation 10b).

larger than the diameter of the absorbing area to the surroundings. Consequently, a temperature elevation on a macroscopic level is expected. Therefore, hot spots at microscopic dimensions of < millimeter scale with no macroscopic temperature elevation are very unlikely according to our physical analysis.

Applying Equations (6c) and (9), we calculated θ_{max} for the two tumor models. Interestingly, the same formula was used and the (local) SAR values (for either heating of the sphere with diameter d or the ECF of width d_e) were inserted. To be more specific, we defined the 'critical lesion diameters' d_c as the minimum d or d_e required to achieve an effective temperature of 43.5 °C or higher in the center, i.e., $\theta_{max} \geq 6$ °C, for a given SAR (assuming a systemic temperature of 37.5 °C). The relationship between d_c and SAR is given by the following simple formulas:

$$d_c[\text{cm}] = (6/0.021/SAR[\text{W/kg}])^{1/2} = 16.90/SAR^{1/2} \quad (10a)$$

or

$$SAR = 285.6/d_c^2. \quad (10b)$$

Figure 6 illustrates the dependency between d_c (referring to the models of Figures 1 and 2) and SAR. For difficult-to-heat tumors, we expect only 10 W/kg in the lesion. Hence, we need large necrotic areas (d_c>5 cm) in order to obtain effective temperatures (>43 °C) using such low RF levels. For easy-to-heat tumors with very high SAR, the obtained d_c approaches one centimeter. However, extremely local SAR peaks >1000 W/kg are required for tiny d_c of a few millimeters. Such high SAR levels are unlikely to be achieved even if the SAR is increased by AM modulation. Finally, for submillimeter dimensions, e.g., 100 µm, excessive SAR peaks $>10^6$ W/kg are required to generate a significant hot spot. We can quickly deduce from Equation (10b) that, for targets (e.g., proteins) in a cell membrane of ~10-nm size, SAR levels of $>10^{14}$ W/kg are required in order to generate a temperature-dependent effect. This is clearly an unrealistic requirement.

Discussion

The AM-RF radiation technique is reported to employ RF for heating (here, 13.56 MHz) as well as VLF radiation (1 Hz to 10 kHz). The latter employs a completely different mechanism to dissipate energy *via* currents in a conductive medium and may enhance the SAR in aqueous tumors. This additional intratumoral power deposition SAR_{TM} (VLF) requires demodulation and is said to be locally restricted to malignant cells because of the specific microenvironment frequently found in tumors and the peritumoral area [19]. For our theoretical analyses, we assumed a considerably higher power in the extracellular space according to a simplified tumor model (Figure 2). Note that, to identify an appropriate VLF range for optimization of this selective effect, matching procedures may be useful [28]. Further, for demodulation, we require a rectifying component; this is obviously accomplished by cell membranes in contact with the extracellular space. Notably, the effects of different frequency ranges have been applied

for therapeutic ultrasound through modulation with a lower frequency [31], even though that mechanism is completely different to the mechanism discussed here.

In the preclinical studies cited above [14–18], a higher cell kill (determined by various surrogate parameters) was achieved with application of the mEHT technique in comparison with water bath heating or RF heating, through adjustment to achieve the same (mean) temperature in the specimens (i.e., cell suspensions, experimental tumors). These phenomena were overwhelmingly explained *via* the hypothesis that small (undetected) hot spots occur in the mEHT experiment. Some researchers have hypothesized that cell kill occurs on a millimeter scale, while the mean temperature in the reference point remains almost constant.

However, our physical analysis suggests that such temperature-dependent effects cannot fully explain the data. According to Figures 5 and 6, relevant temperature increases on a millimeter (or even sub-millimeter) scale are improbable, because unrealistic SAR delta peaks are required, e.g., $SAR > 10{,}000$ W/kg for a sphere of 1-mm diameter. Even for a sphere of 1 cm, already having macroscopic dimensions, the SAR is either very high (>200 W/kg) or the temperature increase is only a few degrees Celsius (~2 °C for 100 W/kg); this increase is insufficient for cell damage. Furthermore, the temperature increase has a range of several d of the heated lesion in all directions (Figure 5) and, therefore, a measurable macroscopic temperature increase should also occur. According to Figure 2, this conclusion is even valid for an aqueous tumor, if the SAR peak of diameter d is replaced by a much more extended network of width d. Thus, we find the same limitations. Note that Figure 2 presents the most optimistic tumor model with respect to microscopic heating effects. Heterogeneities and tumor stroma typically reduce the power deposition in the extracellular space and further limit the temperature-dependent effects.

In summary, we cannot exclude a slight circumscribed temperature increase of a few degrees Celsius. However, these slight inhomogeneities of the temperature distribution cannot explain the extremely large differences in cell kill. The discussion of 'point heating' is not new [32], and is still implicitly proposed if temperature-dependent biological effects are postulated in the absence of bulk heating. A similar discussion has again arisen using the buzzword 'nanoheating', which has essentially the same meaning as 'point heating'. Nanomedicine researchers have evaluated heating of a single cell or a microscopic cell cluster to a cytotoxic temperature through use of intracellular nanoparticles [33,34]. Realistic estimations of the expectable nanoparticle power absorption indicate that we are far from heating of a single cell, because the required intracellular SAR would exceed one million Watts per kilogram for a region of <100 µm, according to Figure 6 [6]. For a region of 10 nm, which is most likely intended in the context of nanoheating, trillions of Watts per kilogram ($>200 \times 10^{12}$ W/kg) are required to achieve a corresponding temperature increase of 6 °C, according to Equation (10b).

Next, the possibility of non-temperature-dependent effects can be considered. In the VLF range, ion movements at and through the membranes may cause chemical imbalances. If so, the local cell environment affects the extent and impact of any chemical stress. For example, electrochemical effects may occur more easily in the tumor microenvironment with its wide ECF network (Figure 2). The discussion of non-thermal effects on viable cells in general [35–37], and of VLF electromagnetic fields in particular, has a long history [38–40]. The resting potential along the cell membranes (–90 to –50 mV along <10 nm) generates an extraordinarily high E field of 10^7 V/m. The common consensus is that we require $E > 1000$ V/m to exceed the thermal noise. Such E fields are beyond the therapeutic level (Table 1). However, the minimum field strength (the so-called 'thermal noise limit') necessary to achieve a cell response remains unclear. Different sophisticated electrical models of the membrane have provided completely diverging estimations of the electric noise [38–40], indicating the complexity of this issue. However, the thermal noise limit is a key parameter if non-equilibrium external signals must be comparable to the thermal noise [41]. Obviously, the presence of pumps, transporters and channels (pores) embedded in a lipid bilayer must be considered in a valid theory, but this field is still largely unexplored. Therefore, 'guided' nonequilibrium VLF currents as induced in the tumor microenvironment may have a much stronger effect on the living cells than expected. One search strategy for non-temperature-dependent effects involves investigations conducted on various ion channels (e.g., potassium or calcium), which demodulate the AM-RF and may be influenced/triggered/modified by the VLF E fields according to their specific functionality.

Previously, Szasz et al. [42] analyzed the consequences of depositing the power in the extracellular medium and postulated a heat flow that would induce various non-equilibrium thermal microprocesses. However, on a microscopic scale of 10 nm (cell membrane) to 10 µm (cell diameter), the relaxation times (Table 1) are very short, enforcing thermal equilibrium after nanosecond to millisecond periods. We conclude that, after power activation, a microscopic temperature distribution steady state is achieved within some milliseconds; hence, our steady state analysis is valid. Recently, Papp et al. [43] suggested that the non-temperature-dependent effects of mEHT can be explained by considering E field interactions with lipid rafts, which arise more frequently in some tumor cell membranes than in normal tissue [44]. However, no experimental validation exists for this asserted mode of action.

In summary, the existence of non-temperature-dependent effects during mEHT is under debate as the specific proof still awaits experimental substantiation. Because mEHT is typically performed at low power levels (e.g., 130 W in [12]), the achieved temperatures are probably also low (e.g., 38–39 °C). Typically, they are not measured. Therefore, the label 'hyperthermia' is probably misleading and could be replaced by 'electromagnetic treatment' or the like.

Conclusions

In this study, a possible additional effect of VLF-AM modulation of a carrier RF in tumors was evaluated from physical

principles. Hence, we found that temperature-dependent mechanisms cannot be involved. Further investigations are recommended to evaluate the possible occurrence of non-temperature-dependent effects involving membranes and the local cell environment.

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Disclosure statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Verkannter side-effect der Hochpräzisions-Radioonkologie

Vom Abskopaleffekt zur Abskopaltherapie – Provozierte Spontanremissionen als neue Immuntherapie bei Krebs

Teil I: Abskopaleffekte in der Onkologie, Vorwort und Einführung
Teil II a: Fallbezogene Abskopaltherapie mit provoziert radiogenem Abskopaleffekt entsprechend einer radiogenen autologen spezifischen Immuntherapie (RASI)
Teil II b: Weitere fallbezogene Darstellungen der Abskopaltherapie
Teil III: Literaturvergleich und Diskussion

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Vom Abskopaleffekt zur Abskopaltherapie – Provozierte Spontanremissionen als neue Immuntherapie bei Krebs

Teil I: Abskopaleffekte in der Onkologie, Vorwort und Einführung

Wulf-Peter Brockmann, Institut OncoLight®

Werden Malignomherde (Primärtumor, Lokalrezidiv oder Metastasen) onkologisch gezielt angegangen und vernichtet, so ist manchmal zu beobachten, dass im Anschluss auch nicht (mit-)behandelte Rezidivtumore oder Metastasen verschwinden. Man spricht dann von Abskopaleffekten, die zwar von allen Beteiligten freudig zur Kenntnis genommen werden, aber in ihrer Genese allenfalls von immunologisch interessierten Kollegen ätiologisch nachvollziehbar sind. Diese zweiteilige Artikel serie geht der Frage nach, ob Abskopaleffekte gezielt ausgelöst werden können und dann nicht mehr nur als Spontanremissionen einzuschätzen sind.

Könnte man wie der Autor tatsächlich davon ausgehen, dass bestimmte Voraussetzungen kumulativ den Eintritt von Abskopaleffekten regelmäßig, wenn auch in unterschiedlicher Ausprägung, ermöglichen oder auch nur begünstigen, so müsste es auch anderen Kollegen (insbesondere Radioonkologen) möglich sein, als Therapiemaßnahme methodisch gezielt Abskopal effekte auszulösen – mit der Konsequenz von Remissionen oder gar Heilungen auch systemisch fortgeschrittener Malignome. Früher hätte man solche eher sporadischen und nicht gezielt provozierten Behandlungsergebnisse (ohne Kenntnisse und Erfahrungen in der Immunologie) als unerwartete und unvorhersehbare Spontanheilungen abgetan.

Wichtige Voraussetzungen zur Provokation von Abskopaleffekten:

1. Ein möglichst intaktes zelluläres Immunsystem,
2. eine Mindestmasse von Krebsgewebe, welches
3. so schnell abgetötet wird, dass seine malignen Zellen nicht mehr die Möglichkeit haben, ihr Apoptoseprogramm anzuwerfen, sondern
4. praktisch mit all ihren antigenen Eigenschaften (auch in der Nähe von Immunzellen wie Dendritischen Zellen) amorph werdend lysieren und somit
5. zuvor nicht in Gänze von Fresszellen beseitigt werden konnten.

Auslösung von Abskopaleffekten durch Radiotherapien mit höchsten Einzeldosen

Bei nomofraktionierten Radiotherapien von Malignomen mit nur 1,8 bis 2,0 Gy Einzeldosis, die sich im Standardfall über Wochen hinziehen, ist die Einzeldosis so gering, dass den bestrahlten, tödlich geschädigten Tumorzellen noch ausreichend Zeit bleibt, bei suffizienter Schädigung ihren eigenen Zelltod per Apoptoseprogramm einzuleiten. Anschließend können sie von Fresszellen beseitigt werden.

Dagegen ist bei der Durchführung von Hochdosis-Strahlentherapien, wie sie in Gammaknife-Zentren, Cyberknife-Zentren und in Radioonkologie-Instituten mit stereotaktischen Hochpräzisionsgeräten in Einzeldosen von 15 bis > 20 Gy jeweils an ein oder maximal zwei Tagen in kurzem Zeitabstand appliziert werden können, im Ziel volumen in der Regel eine ausrei chend große Tumorzellmasse vor handen, deren Zellen nach ihrer Bestrah lung so schnell absterben, dass ihnen nicht einmal genug Zeit bleibt, in Apotose zu gehen. Bildlich gesprochen zerfließen sie mit dem gesamten Schatz antigener Eigenschaften ihrer Zelloberflächen-Moleküle und ihres Inneren in ihre Umgebung. In diesem Milieu können Immunzellen nun so viele dieser antigenen Botschaften als fremd erkennen,

einsammeln und weiteren Immunzellen präsentieren, dass diese schließlich auch anderweitig im Körper von Patienten gleichartige maligne Zellen als fremd wahrnehmen und vernichten.

Ähnlichkeiten zwischen einer Cyberknife-induzierten, immunbasierten Abskopaltherapie und einer Autologen Spezifischen Immunisierung (ASI)

Bei einer ASI werden entnommene Tumorzellen abgetötet und zu einer vakzinierbaren Suspension verarbeitet, die es erlaubt, einen Großteil ihrer Antigene den passenden Immunzellen des Patienten zu präsentieren und so eine Kaskade im Immunsystem auszulösen, an deren Ende im günstigsten Falle die vollständige Tumor- und Metastasenvernichtung steht.

Abb. 1: Das Cyberknife M6, ein robotergestützter Linearbeschleuniger

Innerhalb der letzten Novellen des Arzneimittelgesetzes (AMG) hat man unter Vorgabe des Patientenschutzes die Herstellung von ASIs unter die Herstellung sogenannter Neuer ArzneimittelTherapieprodukte (ATMPs) subsumiert. Tumorzellen von operablen Krebs- Patienten können aber zurzeit unter Wahrnehmung ihrer gesetzlich verbrieften freien Arztwahl (sprich: Wahl des Chirurgen) in aller Regel nicht GMP-gerecht gewonnen werden: Klinik, Ope rateur, Operationssaal etc. wären nämlich hierfür GMP-konform zu zertifizieren und sind deshalb kaum vorhanden.

ASIs aus autologem Krebsgewebe als „Wirkstoff" müssen aber ausnahmslos wie alle anderen ATMPs GMP-zertifiziert hergestellt werden und konnten daher mangels realistischer AMG-konformer Tumorzellentnahme und -verarbeitungsmöglichkeiten seit einigen Jahren erfolgreich aus der Krebstherapie verbannt werden.

Insofern ist es zu begrüßen, dass man auch radioonkologisch, quasi „ferngesteuert", per Gammaknife, Cyberknife oder evtl. sogar stereotaktisch noch direkt im Patienten und nicht erst per Vakzinierung nach operativer Entnahme und Zubereitung autologer Tumorzellen auf Laborwerkbänken jenseits der „Roten Linien des AMG" eine analoge Form von ASI auslösen kann, ohne dass das AMG dies zu verhindern vermag, und wogegen die aktuellen Strahlenschutzrichtlinien (vorerst) noch nicht vereinnahmt worden sind.

Ausblick

Im zweiten Teil dieser Artikelserie zur möglichen Induktion von Abskopaleffekten als Abskopaltherapie im Sinne eines gezielten Nebeneffekts der Hochdosis- bzw. Hochpräzisionsstrahlentherapie werden vom Autor als Radiologen und Radioonkologen und dank langjähriger Tätigkeit in der Immun-Onkologie mit Dendritischen Zellvakzinierungen auch Fälle eigener erfolgreicher Abskopaltherapien bei Krebspatienten, also Fälle mit bewusst – und dabei quasi ohne Nebenwirkungen – herbeigeführten Abskopaleffekten bis hin zu möglichen Heilungen, umfänglich dargestellt und ausführlich diskutiert werden.

Die Analyse der Kasuistik wird zeigen, dass bei einigen Patienten, bei denen gezielt und faktisch ohne Nebenwirkungen Abskopaleffekte ausgelöst wurden, umfangreiche Wirkungen erzielt werden konnten, die bis zu Vollremissionen und möglichen Heilungen reichten.

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Verkannter side-effect der Hochpräzisions-Radioonkologie

Vom Abskopaleffekt zur Abskopaltherapie – Provozierte Spontanremissionen als neue Immuntherapie bei Krebs

Teil II a: Fallbezogene Abskopaltherapie mit provoziert radiogenem Abskopaleffekt entsprechend einer radiogenen autologen spezifischen Immuntherapie (RASI)

Wulf-Peter Brockmann, Institut OncoLight®

Während in Teil I dieser mehrteiligen Ausarbeitung die prinzipielle Möglichkeit einer Abskopaltherapie und die immunologischen Voraussetzungen für einen erfolgreichen Abschluss mit Teil- oder Vollremissionen beschrieben wurden, soll in diesem zweiten Teil der klinische und diagnostische Verlauf bei einem Patienten mit einem metastasierten malignen Pleuramesotheliom und einer seit nunmehr dreieinhalb Jahren anhaltenden und aus einer Abskopaltherapie hervorgehenden Vollremission aufgezeigt werden.

Das maligne Pleuramesotheliom ist ein von den Mesothelzellen ausgehender bösartiger Tumor der Pleura. Im hier behandelten Fallbeispiel eines Patienten mit metastasiertem malignen Pleuramesotheliom bleiben aufgrund des regelmäßig tödlichen Verlaufs dieser Erkrankung kaum Möglichkeiten offen, das positive Behandlungsergebnis, eine aktuell bereits lang anhaltende Vollremission (s. nachfolgenden PET-CT-Verlauf), anderen Therapieeinflüssen zuzuschreiben, zumal die anfänglichen auswärtigen, von einer Universitätsklinik durchgeführten Therapieversuche den drei schulmedizinisch anerkannten Säulen der Krebstherapie zuzurechnen waren. Diese jedoch hatten beim Erkrankten nur linksseitig im Bereich des Primarius Erfolg, während die Chemotherapie die rechtsseitige

Thorax-Metastasierung nicht verhindern konnte.

Erst die nach Abschluss der Standardtherapie begonnenen erfolgreichen Behandlungsversuche, die seit Jahren von Leitlinienverfechtern als ökonomische Konkurrenz empfunden und nicht zuletzt auch deshalb von systemtreuen Therapeuten bzw. Pharmakoonkologen strikt abgelehnt werden, haben den jetzigen hervorragenden klinischen Zustand des Patienten in seiner Gesamtheit zu verantworten. Würden die Kritiker einer Abskopaltherapie dieses Ergebnis als nicht-abskopalbedingt ablehnen, so müssten sie die übrigen Behandlungen als Ursache des Erfolges anerkennen – oder umgekehrt! Dies scheint eine Zwickmühle für die Kritiker, die allerdings der betroffene Patient nur zu belächeln vermag.

Fallbeispiel Pleuramesotheliom

Fall D.C. (*01/62 männl.), mit Asbestose-bedingtem Pleuramesotheliom li.-seitig (pT4 mit Perikard- und Zwerchfellinfiltration)

Bisherige therapeutische Maßnahmen

Die Standardtherapiemaßnahmen, die der Abskopaltherapie vorausgingen, folgten dem bekannten Schema von Operation, Bestrahlung und Chemotherapie. Die chirurgische Intervention erfolgte im März 2014. Es handelte sich dabei um eine radikale Pneumektomie li. mit teilweiser Perikardektomie und Phrenicoplastik, jeweils wegen pathohistologisch nachgewiesener Tumorinfiltrationen (Abb. 1a und 1b zeigen die Aufnahmen des postoperativen Nativ-CT). Die radiologische Behandlung erfolgte von April bis Juni 2014 als Nachbestrahlung der gesamten li. Thoraxhälfte mit Photonen eines Linearbeschleunigers bis 50 Gy GD, (ED 1,8 Gy), im im Anschluss daran von Juni bis September 2014 die Chemotherapie mit vier Zyklen Pemetrexed- /Cis-Platin.

Das Kontrollergebnis vom September 2014 zeigt die computertomographische Diagnose einer singulären Lungenmetastase re.pulmonal (Abb. 2), im Februar 2015 folgte die Diagnose von 16 Lungenmetastasen re.-pulmonal (Abb. 3).

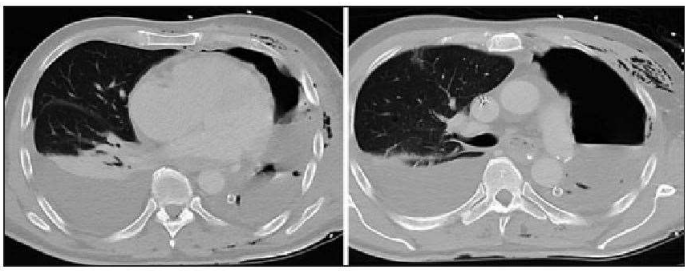

Abb. 1 a, b: Im postoperativen Nativ-CT Seropneu li. und ausgeprägter Reizerguss re.

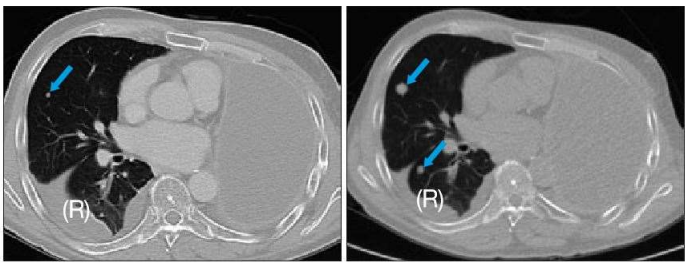

Abb. 2: Re.-pulmonale Metastase im Nativ-CT (blauer Pfeil) und Resterguss (R)

Abb. 3 (rechtes Bild): Zwei von 16 re.-pulmonalen Metastasen im Nativ-CT (blaue Pfeile) und Resterguss (R)

Interimstherapie vor Abskopaltherapie-Versuch Der Patient lehnte den Vorschlag einer Zweitlinien-Chemotherapie ab und entschied sich stattdessen für folgende Kombinationstherapie von Februar bis Mai 2015:

a. Dendritische Zell-Immuntherapie-Vakzinationen in einem 4- bis 6-wöchigen Intervall.
b. Kombiniert wurde diese regelmäßig zwei- bis dreimal pro Woche mit Radiowellen-induzierten kapazitiven lokoregionalen ThoraxBehandlungen (Oncothermie), bestehend einerseits aus milder Hyperthermie (Wirkung etwa 20 % der Gesamtwirkung) und elektromagnetischen Wechselstromfeldern (Wirkung etwa 80 % der Gesamtwirkung).
c. Hinzu kamen Lowdose-Chemotherapien mit 50 mg Endoxan täglich (1 Tbl. abends über etwa acht Wochen hinweg) sowie mehrfache Lowdose-Chemotherapie-Zyklen, bestehend aus jeweils 50 mg Cardioxane (i.v. Kurzinfusion Tag 1), 2 mg Vinblastinsulfat (i.v. Bolusinjektion Tag 2) und 50 mg Cardioxane (Kurzinfusion Tag 3).

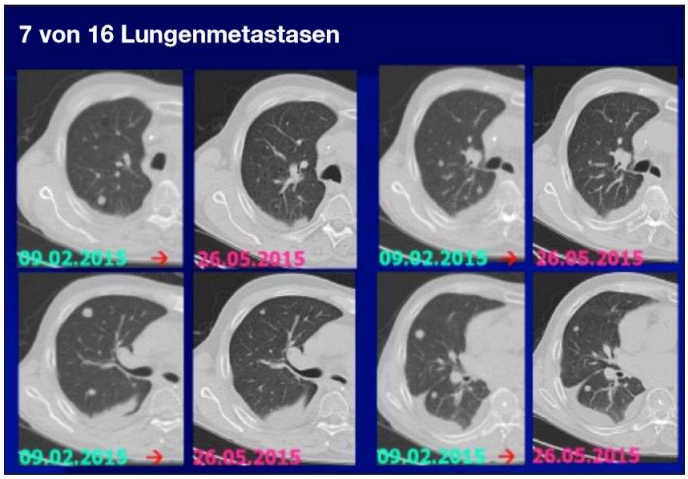

Abb. 4: Kontrollergebnisse, computertomographisch 02/15 und 05/15 betr. 7 der 16 Lungenmetastasen; größenbezogene Teilremission der Metastasen, ohne Auftreten neuer Herde

Gesamtresultat der präabskopalen Therapie

Bis März 2015 war computertomographisch eine hochgradige Verkleinerung oder völlige Beseitigung der 16 Lungenmetastasen erkennbar. Im Februar 2016 zeigte das PET-CT (bei Vollremission der übrigen 15 Metastasen) einen singulären LungenmetastasenProgress und das Neuauftreten eines lokal umschriebenen, jedoch aufgrund von Größe und wegen des Umfangs der Standard-Vorbehandlungen nicht mehr bestrahlbaren bzw. operablen, rechtsseitigen Pleuramesotheliom (Abb. 5 a,b / 6 a,b).

Es erfolgte umgehend eine radioonkologische Abskopaltherapie: die Cyberknifetherapie mit 2 × 15 Gy fand Metastasen-umgreifend statt ohne anderweitige systemische oder gezielt lokale Behandlung des re.-seitigen umschriebenen Mesotheliomrezidivs an der Thoraxwand. Jedoch wurden die monatlichen DC-Vakzination und zwei- bis dreimal wöchentlich jeweils einstündige Elektrohyperthermie-Sitzungen fortgesetzt. Es folgten keine weiteren chirurgischen Eingriffe oder Niedrigdosis-Chemotherapie-Anwendungen.

Ergebnis der Abskopaltherapie

Die Beseitigung der Lungenmetastase mithilfe der Cyberknife-Behandlung war erfolgreich, per Abskopaleffekt gilt dies auch für die Remission des Pleuramesotheliomrezidivs – es liegt eine anhaltende Voll remission bei fehlender lokaler Glucoseutilisation vor (Abb. 7 a,b / 8 a,b). Dies ist der Stand bis mindestens November 2018, als das letzte PET-CT vorgenommen wurde, und klinisch seit aktuell nunmehr über 40 Monaten. Im November 2018 liegt also eine gute Remission mit weiterhin kleinem Weichteil-Plus im ursprünglichen Lungenmetastasen-Bereich vor (Abb. 9 a), jedoch wiederum Vollremission bezüglich FDG-Speicherung in Region der Metastase (Abb. 9 a) und des Mesotheliomrezidivs (Abb. 9 b) bei einer dortigen Glucoseutilisation in Höhe von nur 0,57 SUV bis 1,85 SUV.

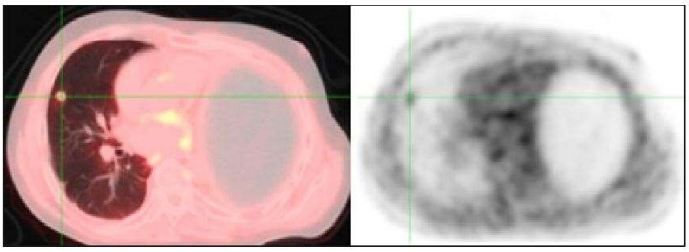

Abb. 5 a (links): 02/16 FDG-aktive Lungenmetastase im PET-CT
Abb. 5 b (rechts): 02/16 FDG-aktive Lungenmetastase im PET

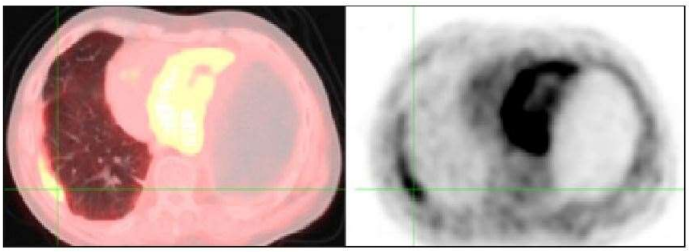

Abb. 6 a (links): 02/16 FDG-aktives Mesotheliomrezidiv im PET-CT
Abb. 6 b (rechts): 02/16 FDG-aktives Mesotheliomrezidiv im PET

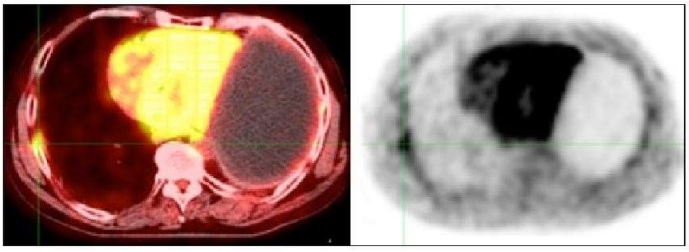

Abb. 7 a,b: 08/16 gute Remission mit nur noch kleinem Mesotheliomrezidiv-Rest; links: im PET-CT, rechts: im PET

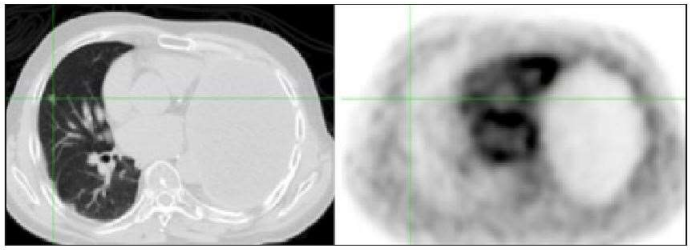

Abb. 8 a,b: 08/16 sehr gute bzw. Vollremission mit nur noch kleinem Lungenmetastasen-Fibrose-Rest ohne FDG-Speicherung: siehe jeweils das Fadenkreuz, links: im PET-CT, rechts: im PET

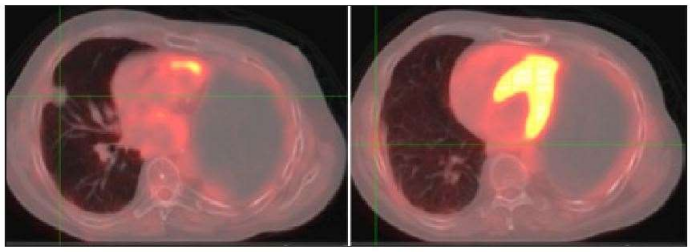

Abb. 9 a, b: linkes Bild zeigt Lungenmetastase im PET-CT (nur Fibrose-Rest?); rechtes Bild zeigt kein Mesotheliomrezidiv mehr (November 2018)

Zukünftige Therapieplanung

Zurzeit hat ohne anderweitige Therapiemaßnahmen und insbesondere ohne einen weiteren Abskopaltherapieversuch eine zahlenmäßige Ausdünnung der DC-Vakzinationen und Elektrohyperthermie-Behandlungen begonnen. PET-CT-Kontrollen sollen auch zukünftig nur einmal jährlich routinemäßig im November stattfinden, solange sich der hervorragende klinische Zustand des Patienten nicht verschlechtert, bzw. solange die klinische Vollremission anhält.

Resümee

Besonders markant im Rahmen möglicher Ergebnisse von Abskopaltherapien erscheint ihr großer Nutzen im Verhältnis zu ihrem Mangel an Gefährdungs- und Nebenwirkungspotenzial, was auch aus den dargestellten Fällen des dritten Teils (II B) der Abhandlung ersichtlich werden wird. Hier wird dann auch die Literatur zur radiogenen autologen spezifischen Immuntherapie (RASI) diskutiert werden können.

Dass sich beim Patienten mit einer einzigen RASI ein so lang anhaltendes Therapieergebnis erzielen ließ, kann unter anderem sicherlich darauf zurückgeführt werden, dass der Patient zum Zeitpunkt dieser Behandlung schon ein seit mehreren Monaten infolge der DC-Therapie optimiertes zelluläres Immunsystem aufweisen konnte. Ob diese Therapie schon direkt im Anschluss an die gescheiterte Chemotherapie den gleichen Erfolg gehabt hätte, lässt sich insofern bezweifeln. Hinzu kommt, dass die zu beseitigende Tumormasse relativ gering war. Indizien für die Richtigkeit dieser Annahmen ergeben sich im letzten Teil der Abhandlung aus weiteren Behandlungsfällen mit inoperabel großer Tumormasse, mit hohem Metastasen-Rezidivrisiko und somit schlechter Prognose, die nur dank wiederholter RASI analog zu den früheren ASI (siehe Teil I) zumindest zeitweise kontrollierbar zu sein schien. Die geschilderten Behandlungen sind dabei sämtlich ohne erwähnenswerte Nebenwirkungen durchgeführt worden, dies steht im Gegensatz zu medikamentösen Dritt- oder gar Viertlinien-Therapien, die darüber hinaus geringere Erfolgsquoten aufweisen dürften.

Dass es praktisch ohne erwähnenswerte Risiken möglich sein könnte, allein durch eine vergleichsweise preiswerte lokale Behandlung eine syste mi sche Wirkung zu erzielen, die sich über die Wirkung bisheriger systemischer Leitlinientherapien hinaus erfolgreich gegenüber einem systemischen Malignombefall erweist, dürfte die Vorstellung vieler Kollegen sprengen, die bislang keine wesentlichen Kontakte zum komplizierten Räderwerk der Immunologie pflegen. Andererseits bein hal ten erfolgreiche, gezielt auslösbare RASI auch ein enormes ökonomisches Sprengstoffpotenzial, da sie nicht in die heutige

medizinpolitische Landschaft zu passen scheinen, in der onkologische Behandlungserfolge bei systemischem Tumorbefall offenbar nur noch durch teuerste Antikörper und Hemmstoffe erzielt werden dürfen, auf dass die Onkologie auch künftig ökonomisch berechenbar bleibt – einseitig Inte res sen-gesteuert.

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Verkannter side-effect der Hochpräzisions-Radioonkologie

Vom Abskopaleffekt zur Abskopaltherapie – Provozierte Spontanremissionen als neue Immuntherapie bei Krebs

Teil II b: Weitere fallbezogene Darstellungen der Abskopaltherapie

Wulf-Peter Brockmann, Institut OncoLight®

Nach den beiden vorangegangenen Teilen dieser Publikation als Teil I sowie Teil II a sollen in diesem Teil II b weitere fünf Fälle mit Ergebnissen möglicher Abskopaltherapien vorgestellt werden. Hieraus resultierende eigene Erkenntnisse unter Berücksichtigung der vorliegenden Literatur werden im abschließenden Teil III diskutiert.

Fall 1: F.W. (*03/50 männl.), mit Asbestose-bedingtem Pleuramesotheliom re. (T4, mit umgreifendem Befall der gesamten Pleura)

Bisherige therapeutische Maßnahmen

Es gab keine chirurgische Behandlung, 04/16 fanden nur Biopsien und Talkumpleurodese statt; es lag eine Inoperabilität aufgrund zu großer Ausdehnung des Pleuramesothelioms der rechten Lunge über sämtliche Pleura-Anteile hinweg vor. Es gab auch keine radioonkologische Behandlung, nur Radiotherapie der Drainagestellen (04 bis 05/16) zur Verhinderung von Implantationsmetastasen (wegen der zu großen Primärtumor-Ausdehnung und demzufolge auch zu großer Pneumonitisrisiken im Falle ausreichend großer Zielvolumina und adäquat hoher Strahlendosen bei Radiatio des gesamten Pleurabefalls rechtsseitig). Medikamentös fand von 06 bis 10/16 die (frustrane) Durchführung einer Cis-Platintherapie/Pemetrexed statt. Insgesamt fünf Zyklen, wegen Unverträglichkeit wurde die Behandlung abgebrochen. Zusammenfassung: Ein anhaltender Tumorprogress ohne sinnvolle Anwendungsmöglichkeit weiterer pharmakologischer Behandlungen.

Interimstherapie vor Abskopaltherapie

Der auswärtige Vorschlags einer Zweitlinien-Chemotherapie wurde patientenseits abgelehnt. Es folgte stattdessen die Durchführung

a. einer dendritischen Zell-Immuntherapie in regelmäßiger Kombination mit
b. einer Radiowellen-induzierten Behandlung, bestehend aus Hyperthermie und elektromagnetischen Wechselstromfeldern (Oncothermie) und
c. Lowdose-Chemotherapien mit 50 mg Endoxan (1 × abends) sowie mit mehrfachen Lowdose-Chemotherapien-Zyklen aus jeweils 50 mg Cardioxane (Tag 1), 2 mg Vinblastinsulfat (Tag 2) und 50 mg Cardioxane (Tag 3).

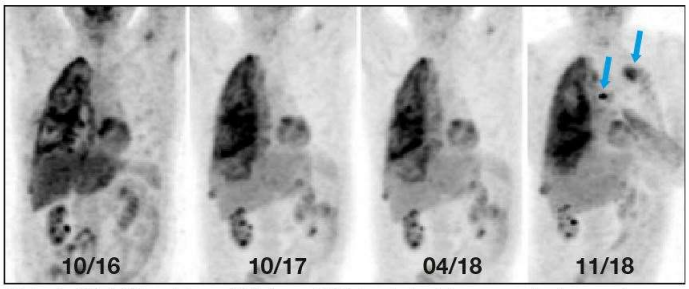

Abb. 1: PET-CT zeigt zweijährigen Stillstand des Tumorwachstums, aber leichten Progress im Nov. 2018; Pfeile: Artefakte aus den Armen und Händen

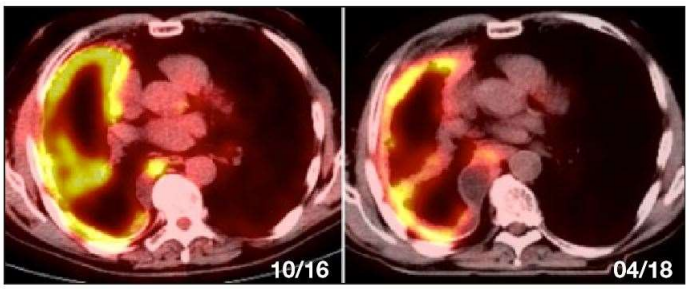

Abb. 2: PET-CTs im Querschnitt mit Therapie-bedingt abnehmender (radioaktiver) Glucose-Utilisation der Pleura zwischen Oktober 2016 und April 2018

Ergebnis: Klinisch und im PET-CT waren zwei Jahre lang (10/16 bis 11/18) im Wesentlichen ein Stillstand des Tumorwachstums bei recht guter Lebensqualität erkennbar (Abb. 1 und 2). Danach wurde labordiagnostisch ein AFP- und M2PK-Anstieg festgestellt sowie im PETCT 11/18 ein diffuser Primärtumorprogress rechtsseitig mit Verringerung der Lungen-Restkapazität, Pleuraerguss li. und erstmaligem Auftreten von multiplen Lungenmetastasen linksseitig bei allgemeiner, schnell progredienter klinischer Verschlechterung (Abb. 3 u. 6a).

Erste radioonkologische Abskopaltherapie

Die erste Cyberknifetherapie (01/19) erfolgte mit 1 × 20 Gy umgreifend auf der 70 % Isodose eines 1,5 cm großen Zielvolumens innerhalb des Tumorbulks rechtsseitig, ohne weitere lokale Strahlentherapiebehandlung des Mesothelioms. Es folgte die Fortsetzung der jeweils einstündigen monatlichen DC-Vakzinationen und regelmäßigen Elektrohyperthermie-Sitzungen, aber ohne weitere chirurgische oder Niedrigdosis-Chemotherapie-Anwendungen. Ergebnis: Fast vier Monate lang (bis Mai 2019) lag eine Teilremission der Lungenmetastasen links und des Pleuramesotheliomrezidivs vor, im PET-CT vom 24.04.2019 gut erkennbar (Abb. 4 u. 6b), ebenso eine Abschwächung der Glucoseutilisierung unter hochgradiger klinischer Besserung aller Symptome sowie der krankheitstypischen Laborparameter: Gewichtszunahme um 5 Kilogramm, bis Mai 2019 kaum noch Hustenreiz, Verringerung der Tumormarker M2PK und AFP, Zunahme des Hb-gehalts, Verringerung der Thrombozytenanzahl von 1 Mio. auf < 0,5 Mio. (erstmalig überhaupt), deutliche Verlängerung der Zeitintervalle zu PleuraergussEntlastungspunktionen linksseitig auf weniger als einmal pro Monat.

Aus Therapieerfolg resultierende, nur teilweise realisierte Therapieplanung

In Abhängigkeit von der klinischen Remissionsdauer wurden Wiederholungen der abskopalen Cyberknife-Therapie und eine Fortsetzung der DC-Behandlungen in Kombination mit Radiofrequenzhyperthermien zur Verlängerung der vorerst wiedererlangten Lebensqualität angestrebt. Dies ist durchaus analog zur Autologen Spezifischen Immunisierung (ASI), die in Fällen einer so großen Primärtumor-Ausdehnung und -progredienz ebenfalls mehrfache Applikationen erfordert hätte. Geplant war evtl. auch die Fortsetzung der abskopalen Cyberknife-Behandlungen innerhalb der rechtsseitigen, noch PET-CT-positiven Mesotheliom-Formationen, zusammen mit einer

Fortsetzung der DC-Impfungen und Radiofrequenzhyperthermien der Thoraxregion, möglichst unter Verlängerung der Therapieintervalle.

Die Umsetzung dieser Therapieplanung folgte bei klinischem Progress ab ca. Mitte Mai 2019 mit leichter Zunahme des Mesotheliombedingten Hustens, der Laborparameter und der PET-CT-Befunde. Es wurde eine zweite radioonkologische Abskopaltherapie angestrebt: Cyberknife-Therapie 05/19 mit 2 × 15 Gy umgreifend auf der 70 % Isodose eines 1,5 cm großen Zielvolumens innerhalb des Tumorbulks.

Ergebnis: Es folgte eine nochmalige klinische Teilremission, jetzt knapp vier Monate lang bis August 2019 anhaltend (Abb. 5). Der Patient konnte in dieser Zeit mit seiner Ehefrau zusammen eine private, mehrwöchige SkandinavienReise mit dem Caravan hoch bis zum Polarkreis realisieren. Ende August 2019 zeigte sich ein bereits über Laborparameter und klinische Symptomatik vermuteter und im PET-CT verifizierter Tumorprogress mit Verlegung des Ösophagus durch eine paraösophageale Lymphknotenmetastase (Abb. 6c). Daraufhin folgt der Beginn einer parenteralen nächtlichen Ernährung sowie einer radio onkologischen hyperfraktioniert-akzelerierten Chemoradiotherapie am konventionellen Linearbeschleuniger mit 2 × 1,2 Gy/die bis kumulativ 44,4 Gy.

Zwei Tage vor der nachfolgend geplanten Abskopaltherapie erfolgte der plötzliche häusliche Tod des Patienten innerhalb weniger Minuten. Am ehesten ist dies erklärbar nach paraneoplastischem Wiederanstieg der Thrombozyten (> 0,5 Mio./ml) infolge einer fulminanten Lungenembolie als typische, Malignom-assoziierte Komplikation (eine Sektion fand nicht statt).

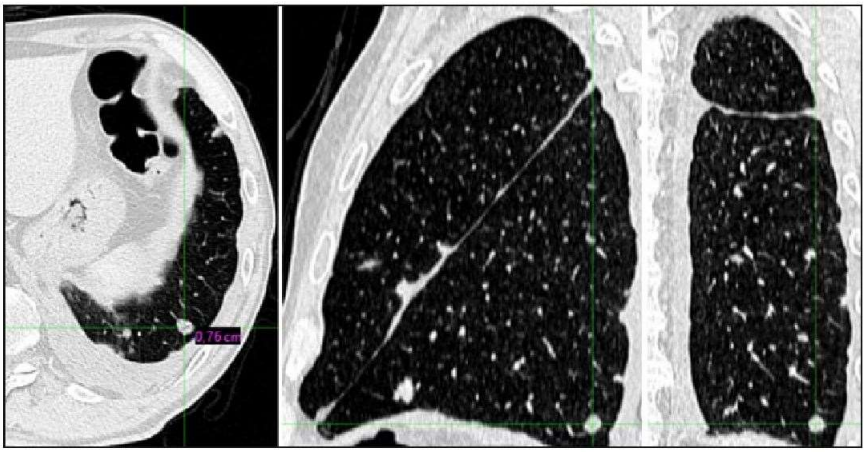

Abb. 3a-c: Nov. 2018, Metastase von ca. 7,5 mm Durchmesser axial, sagittal und koronar

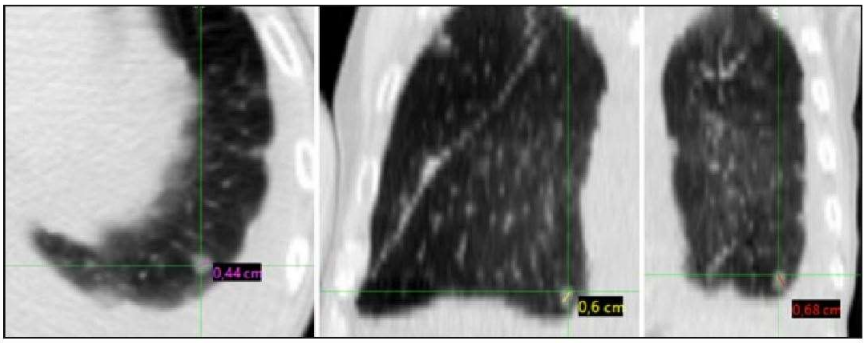

Abb. 4a-c: April 2019, Metastase von ca. 4,5 bis 6,8 mm Durchmesser axial, sagittal und koronar

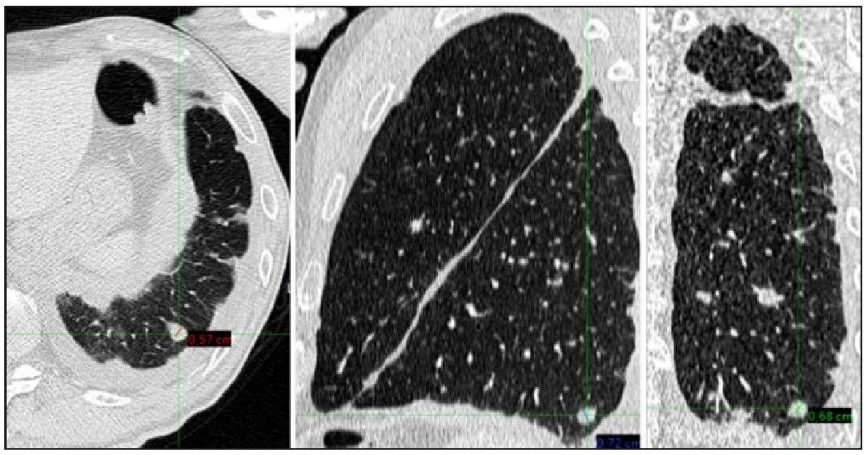

Abb. 5a-c: CT vom Juli 2019, Leitmetastasengröße li. zwischen 5,7 und 7,2 mm axial, sagittal und koronar, kaum Erguss

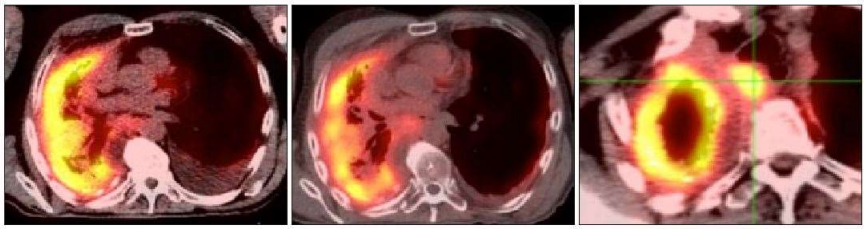

Abb. 6a: PET-CT 11/18 i. Vgl. mit Abb. 2a und b: Progress re. und bei neu aufgetretenem Pleuraerguss auch li.; Abb. 6b: nach 2. Abskopaltherapie nochmals rückläufiger Erguss li. in 07/19; Abb. 6c: Im Fadenkreuz paraösophageale Lymphknotenmetastase (wegen Dysphagie vor konventioneller Strahlentherapie 07/19)

Vier weitere Fälle (Kurzfassung)

Fall 2: M.E. (*10/66, weibl.)

08/00: Primäre operative Entfernung eines malignen nodulären Melanoms der rechten Flanke, Clark Level III, Breslow-Index 1,0 mm.

04/08: Axillarevision re. wegen ausgedehnter Lymphknotenmetastasierung (11 pos. LK´s/20). 08 bis 09: Adjuvant hochdosiertes Alpha-Interferon über elf Monate.

10/10: Erstmaliges Auftreten von 7 Hirnmetastasen, die im selben Monat jeweils mit einer Einmal-Hochdosis per Gammaknife therapiert wurden. Angeschlossen wurde eine dreimalige dendritische Zell-Immuntherapie (unter Verwendung von Poly-IC, onkolytischen Viren und Melanom-Zellbestandteilen).

12/19: Vollremission seit mehr als neun Jahren hinweg anhaltend ohne weitere therapeutische Maßnahmen. (Hinweis: Therapie und Diagnostik dieser Patientin fanden außerhalb der Praxis des Autors statt. Die Unterlagen entstammen einem Sozialgerichtsgutachten dieses Falles und aktuellen Angaben damals behandelnder und heute nur noch die Tumornachsorge durchführender Kollegen).

Fall 3 bis 5: Bei zwei weiteren Patienten, die in der Praxis des Autors behandelt worden sind, wurden mit ca. 1,5 bis 2,5 cm Durchmesser anscheinend ausreichend große Weichteilmetastasen abskopal behandelt, sodass (kurz zusammengefasst) in Fall 3 bei einer Patientin mit einem Triple-neg. G3-Mammakarzinom trotz anfänglicher, vor zweieinhalb Jahren unter anderem radioonkologisch behandelten Filiae im Sternum und multiplen Lymphknotenmetastasen seit der RASI der nachfolgenden hochthorakalen Weichteilmetastase mit einer Cyberknife-Einzeithochdosis (19 Gy auf der 70 %igen Isodosislinie) keine Tumormanifestation mehr vorliegt. Da seit drei Monaten jedoch auch andere prophylaktische Maßnahmen wie dendritische Zell-Immun-Vakzinationen und Großfeld-Radiofrequenz-Hyperthermien (Gerät EHY 3010, Fa. Oncotherm) durchgeführt werden, dürfte man einen sich auch zukünftig fortsetzenden stabilen R0-/M0-Verlauf nicht allein auf die stattgefundene Abskopaltherapie zurückführen, sondern sollte dieser Maßnahme nur eine Teilverantwortung für den Behandlungserfolg überlassen.

Ähnliches gilt für einen weiteren Fall (Fall 4) mit stabilem klinischen Verlauf von Lungen- und Knochenmetastasen über ein Jahr hinweg nach zweimaliger Cyberknife-Abskopaltherapie von Weichteilmetastasen am Oberarm und am Gesäß beim Vorliegen eines metastasierten Nierenzellkarzinoms als Primärtumor unter simultaner Sutentbehandlung und Impfungen mit dendritischen Zellen. So lässt sich auch in diesem Falle der deutlich protrahierte Verlauf wahrscheinlich nur teilweise auf die beiden RASI zurückführen.

Nach einer Abskopaltherapie konnte bei einer weiteren Patientin (Fall 5, Patientin mit einer größeren Lebermetastase eines Gallengangkarzinoms) für rund drei Monate eine klinische Gesamtbesserung und ein zeitweiliger Rückgang von Serumtumormarkern (CA 19-9 und CEA) beobachtet werden, aber hiermit verbunden auch ein darüber hinaus noch mehrere Monate lang anhaltender Rückgang von malignem Aszites und malignem Pleuraerguss. Während vor und nach den drei Monaten Teilremission auch andere Behandlungsmodi wie Radiofrequenz-Hyperthermie-Applikationen zum Zuge kamen (EHY 3010, Fa. Oncotherm), wurden diese während der Teilremission eingestellt und dürften damit weniger für die zeitweilige Besserung der Situation verantwortlich gewesen sein.

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Verkannter side-effect der Hochpräzisions-Radioonkologie

Vom Abskopaleffekt zur Abskopaltherapie – Provozierte Spontanremissionen als neue Immuntherapie bei Krebs

Teil III: Literaturvergleich und Diskussion Wulf-Peter Brockmann, Institut OncoLight®

Wulf-Peter Brockmann, Institut OncoLight®

Um zu verstehen, wie eine RASI funktioniert, kann man auf Fachliteratur aus den 1950er Jahren sowie auf Werke um die Jahrhundertwende zurückgreifen. Dabei kommt man unweigerlich zum Evidenzbericht zur S3-Leitlinie zum exokrinen Pankreaskarzinom und (darin enthalten) zum Stellenwert der Strahlentherapie. In diesem Bericht wird folgende Diskrepanz diskutiert: Einerseits war das Gesamtüberleben von Patienten mit nicht-resektablen Tumoren höher, wenn sie mit IORT (Intraoperativer Radiotherapie) anhand schneller Elektronen behandelt worden waren, als das Überleben von Patienten, die (nur) eine Chemotherapie oder konventionelle Chemo-Radiotherapie erhalten hatten. Andererseits ergab sich keine Verlängerung der Überlebenszeit per IORT, wenn direkt zuvor ein fortgeschrittener Tumor vollständig (R0?) reseziert werden konnte. Die (Einzeit-) Strahlendosen betrugen während der Operation durchschnittlich 30 Gy. Auch eine zusätzlich zur IORT verabreichte Chemotherapie konnte daran nichts verbessern.

Entsprechend verwirrend ist auf den ersten Blick das Fazit innerhalb der genannten Cohorten-Zusammenfassung, in der die Ergebnisse vornehmlich japanischer Autoren als widersprüchlich gewertet wurden: Dass in den einzelnen Arbeiten Patienten mit nicht-resektablen Primärtumoren des Pankreas infolge der IORT im Hinblick auf ihr Gesamtüberleben insgesamt einen Vorteil gehabt haben sollen, erscheint zwar auch dem nicht-immunologisch vorgebildeten Radioonkologen plausibel. Ein wenig befremdlich dürfte ihm aber sein, dass eine zusätzliche Chemotherapie womöglich nichts genützt hat. Ganz unverständlich erscheint es danach jedoch onkologisch tätigen Medizinern, dass eine IORT direkt im Anschluss an eine erfolgreiche Tumorresektion im Vergleich zur alleinigen Resektion keinen Vorteil erbracht haben soll – nicht einmal nach neoadjuvanter Chemotherapie. An genau diesem Punkt ist zu diskutieren, ob der Grund für solch einen Mangel, bezogen auf eine eigentlich zu erwartende Verbesserung der Prognose, vielleicht darin liegt, dass bei Pankreaskarzinom-Patienten die Gesamtüberlebensdauer in erster Linie von der hämatogenen Streuung der Primärtumore, insbesondere in die Leber, sowie einer häufigen (späteren) klinischen Ausbildung einer Peritonealkarzinose abhängt – und weniger vom Risiko eines Lokalrezidiv-Tumors. Die Realität ist, dass sich die Prognose quo ad Gesamtüberleben nach R0-Resektion und angeschlossener IORT nicht verbessert, während das Gesamtüberleben bei nicht-operablen Tumorpatienten von einer IORT hingegen eindeutig profitiert. Dabei ist dieser Widerspruch für einen Immunologen gar kein echter Widerspruch, sondern ein zu erwartendes Resultat, zieht man es als Beweis für die Möglichkeit von Abskopaleffekten infolge lokaler Höchstdosis-Strahlentherapien heran, soweit sie gezielt makroskopisch vorhandenes Tumorgewebe erfassen.

Hier wird die Diskussion mit den Angaben der nachfolgenden Literaturstelle 1 (siehe Kasten) zu einem veritablen Indiz dafür, dass es nach totalen Tumorresektionen direkt im Anschluss an eine IORT gar nicht zu einer Immunreaktion im Sinne einer RASI kommen kann, weil das hierfür zwingend notwendige Substrat fehlt, nämlich florides Tumorgewebe, das im Anschluss an die in kürzester Zeit eingestrahlte Hochdosis der einmaligen IORT nicht mehr zur Apoptose fähig ist, aber mit seinen antigenen Eigenschaften ins Immunsystem eingeht. Dann kann natürlich eine solche IORT im Rahmen einer R0-Resektion direkt nach operativer Entfernung der Immunitätsquelle auch niemals zu einer RASI werden, und folglich auch keinen immunogenen Einfluss mehr auf eine mögliche Leber- und/ oder Peritonealmetastasierung ausüben.

1 Nothacker M, Langer T, Rütters D, Weinbrenner S: Evidenzbericht 2012 zur S3-Leitlinie zum exokrinen Pankreaskarzinom – Stellenwert der Strahlentherapie. Ärztliches Zentrum für Qualität in der Medizin, Berlin 2012; online: www.aezq.de/mdb/edocs/pdf/literatur/evidenzbericht-s3-leitlinie-pankreaskarzinom.pdf

Unter „Ergebnisse der Literaturrecherche zur IORT" findet sich Nagai et al. 2011 (S. 23): Patienten (n = 218) mit lokal fortgeschrittenem Pankreaskarzinom, Japan. Die Patienten wurden zwischen 1995 und 2009 behandelt. Das Gesamtüberleben war bei Patienten mit nicht resektablem Pankreaskarzinom signifikant besser mit IORT (Durchschnitt: Gabe von 30 Gy; $p < 0{,}001$), 58 % dieser Patienten hatten zusätzlich eine Chemotherapie. […] Der Vergleich IORT vs. IORT+CT zeigte keinen signifikanten Unterschied. Patienten mit reseziertem, lokal fortgeschrittenem Pankreaskarzinom zeigten keine Verbesserung des Gesamtüberlebens bei IORT. […] Fazit: Die gefundene Literatur zeigt widersprüchliche Ergebnisse zu den Effekten der IORT in Bezug auf eine Verbesserung des Überlebens und in Bezug auf potenzielle Komplikationen für Patienten mit resektablem Pankreaskarzinom.

Bewertung der Literatur

Diese Angaben wurden dem Autor schon 1992 an einer Universitätsklinik nach dort mehrmals versuchsweise durchgeführter IORT beim Pankreaskarzinom während seiner damaligen Radioonkologen-Tätigkeit von einem im Rahmen des genannten IORT-Programms eingeladenen japanischen Kollegen bestätigt; verwundert war man damals allerdings über dessen mündliche Angaben zu hervorragenden Überlebenszeiten nach IORT bei Pankreaskarzinomen und zu den sehr hoch und fast schon zu hoch anmutenden Elektronen-Strahlendosen von bis zu ca. 40 Gy als Einmaldosen. Aus internen Gründen wurde die IORT an der Klinik des Autors jedoch wieder eingestellt, bevor ausreichend valide Zahlen zu Therapie-Ergebnissen und zu einer Vergleichsmöglichkeit mit den japanischen Angaben vorliegen konnten.

2 Thallinger C et al.: Abscopal effect in the treatment of malignant melanoma. Der Hautarzt 2015; 66(7): 545-548

3 Saba R et al.: Long-term survival consequent on the abscopal effect in a patient with multiple meyeloma. BMJ Case Reports 2016

4 Mole RH: Whole Body Irradiation – Radiobiology or Medicine? British J Radiol 1953; 26(305): 234-241

5 Dewan MZ et al.: Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect, when combined with anti-CTLA-4 antibody. Clin Canc Res 2009; 15(17): 5379-5388

6 Grass GD et al.: The immune mechanisms of abs-copal effect in radiation therapy. Cancer 2016; 40(1): 10-24

In dieser kleinen Literatursammlung gelten Abskopaleffekte als seltene Ereignisse, die man anscheinend noch am ehesten im Rahmen von Melanomtherapien beobachten konnte,2 selten bei Patienten mit multiplem Myelom 3 und in Einzelfällen beim NSCLC (Adenokarzinom), medullärem Schilddrüsenkarzinom, Zervixkarzinom, Merkelzellkarzinom und primären malignen Lymphomen. Die erste Veröffentlichung, die auf die Beobachtung eines Abskopaleffektes direkt eingeht, stammt aus dem Jahr 1953,4 wurde aber während der nachfolgenden Jahrzehnte (!) von anderen Autoren nicht mehr weiter verfolgt, schon gar nicht systematisch – als käme ein solcher Effekt einem nicht kopierbaren Wunder gleich. Tierversuche hierzu wurden erst 2009 publiziert,5 blieben aber ebenfalls jahrelang ohne gebührendes Echo. Ebenso wenig nachhaltig – im Vergleich mit gewinnbringenden Immuntherapien und deren patentierbaren Antikörpern – waren die nachfolgenden Einzelpublikationen mit Bezug auf die unterschiedlichsten Pathohistologien, die dem Phänomen des Abskopaleffektes und seiner Funktionsabläufe ein wenig näher kamen. Wichtig erscheint dem Autor, dass dieser Effekt regelmäßig nur im Zusammenhang mit gleichzeitig stattfindenden Strahlentherapien gesehen wurde.5, 6 Die Publikation zu Tierversuchen 5, die darauf abzielte, dass der Effekt nur infolge fraktionierter Behandlungen und nicht etwa aufgrund von Einzeldosen aufträte, fand in der Humanmedizin keine Bestätigung. In der Humanmedizin, d.h. auch in der Praxis des Autors und innerhalb seines Netzwerks immunologisch tätiger Onkologen, wurden Abskopaleffekte einzig durch ein- bis dreimalige Strahlenhöchstdosen von mehr als 13 Gy Einzeldosis auf der 70 % Isodosis-Linie per Gamma- oder Cyberknife ausgelöst, jedoch in der fast vierzigjährigen radioonkologischen Tätigkeit des Autors bislang niemals im Rahmen einer fraktioniert gegebenen Strahlentherapie mit Normaldosen zwischen 1,5 und 2,5 Gy gesehen.

In der dem Autor als aktuellste hierüber vorliegende Publikation aus Cancerworld 2019 (Riboldi E: Radio-immunotherapy, a work in progress, https://cancerworld.net) weist die Autorin darauf hin, dass der Begriff Immunotherapy beim ESTRO 38 als jährlichem Kongress der Europäischen Gesellschaft für Radiotherapie 132-Mal innerhalb der Abstracts des Kongressbandes auftaucht. Innerhalb der nachfolgenden Absätze ihrer Publikation beginnt sie offensichtlich eine enge Einbindung der Strahlentherapie in die (pharmakoonkologisch induzierte) medikamentöse Immuntherapie anzustreben. Riboldi widmet sich dabei in ihrer Veröffentlichung auch ausdrücklich dem Abskopaleffekt und spricht von nur insgesamt 46 publizierten case reports zwischen 1969 und 2014. Auch sie weist auf die Vielfältigkeit der mitbetroffenen onkologischen Pathohistologien hin, wobei Abskopaleffekte von ihr ebenfalls für Melanome, aber auch für Nierenzellkarzinome, Brustkrebs und hepatozelluläre Karzinome genannt werden. Auch sie geht davon aus, dass der Mechanismus seiner Auslösung im zellulären Immunsystem liegt. Sie sieht jedoch – im Gegensatz zum Autor – die Ursache solcher Effekte hauptsächlich im Freisetzen von Substanzen durch bestrahlte, geschädigte, aber anscheinend noch lebende Krebszellen, die von immunkompetenten Zellen aufgenommen und weitergeleitet werden, bis ein noch ausreichend funktionierendes Immunsystem dann auch diese malignen Zellen und die übrigen, die die gleichen Moleküle (z.B. an ihrer Oberfläche) aufweisen, vernichten kann.

Dies erscheint auf den ersten Blick sicherlich plausibel, erklärt aber nicht, weshalb dieser Effekt so rar vorkommt und auch bei großen Tumoren, in denen schon bei der ersten Fraktion einer normalen Therapieserie mit Dosen in Höhe von 1,5 bis ca. 2,5 Gy eine sehr hohe Anzahl von Tumorzellen geschädigt werden, eigentlich nie gesehen wird. Wird aber im Vergleich unter Zuhilfenahme eigener Erfahrungen des Autors ein kleiner Tumor bzw. eine kleine Metastase von nur 1,5 bis 4 cm Durchmesser innerhalb kürzester Zeit mit einer sehr hohen Einmaldosis von mehr als 19 Gy tödlich getroffen (gilt auch für höchstens ein bis zwei weitere Höchstdosis-Applikationen von 13 bis 19 Gy, falls die ionisierende Strahlung aus unterschiedlichsten klinischen Gründen nur auf diese Weise fraktioniert applizierbar ist), so setzen die Tumorzellen nicht mehr einzelne Substanzen (wie von Riboldi postuliert) frei, sondern quasi mit einem Schlag praktisch ihren ganzen Inhalt, da ihnen nicht einmal mehr die Zeit zur Verfügung steht, die Apoptose einzuleiten. Sie scheinen regelrecht in Richtung aufnahmebereiter dendritischer Zellen zu zerfließen. Insofern dürfte eine zwingende Voraussetzung für eine optimale Erkennung von Tumorzellen durch entsprechende Immunzellen ein Maximum an frei verfügbaren Danger-Signalen sein, die bestimmte T-Lymphozyten, an die dendritische Zellen diese Signale übergeben, nicht als hauseigen erkennen konnten. Nach mengenmäßig ausreichender Klassifizierung der Signale als fremd, können dann jedoch die hierfür vorgesehenen Zellen des zellulären Immunsystems auch anderweitige, nicht mitbehandelte Tumorzellen als fremd und gefährlich wahrnehmen und eliminieren, was makroskopisch im Abskopaleffekt endet, der (eher selten) eine Vollremission ausmachen kann oder auch zeitweise (und wohl viel häufiger, aber als Effekt bislang praktisch immer übersehen) zu einer auch anderweitigen (zeitweisen) Minderung der Tumorzelllast führen kann. Es ist nachvollziehbar, dass auch infolge länger anhaltender, direkt vorangegangener Chemotherapie-Kombinationen nach jeder weiteren frustranen Wahl diverser miteinander kombinierter Zytostatika mit konsekutiver hochgradiger Vorschädigung des Immunsystems dank konsekutiver Lymphozytopenie solche Abskopaleffekte nicht mehr zu erwarten sind. Nach Riboldi kommt es auch in der Kombination von Checkpoint-Inhibitoren, mononuklearen Antikörpern oder auch beispielsweise GM-CSF (Granulozyten-Makrophagen- Kolonien stimulierenden Faktor) mit Strahlentherapien zu Abskopaleffekten in Höhe von bis zu 25 %.

Die letztgenannte Aussage birgt ein großes Risiko: Sie suggeriert dem Leser, sich evtl. teuerster Medikamente im Genre der sog. Immuntherapie bedienen zu müssen, um per Strahlentherapie anhaltende Abskopaleffekte zu erzielen. Daraus erwüchse die Gefahr, dass sich die Radioonkologie einmal mehr von der Pharmakoonkologie die Regie ihrer Behandlungen sukzessive aus der Hand

nehmen ließe. Leitlinien würden dann nur noch Kombinationen von Strahlentherapien und Immunmedikationen (ATMPs) zulassen, um Abskopaleffekte zu erzielen. Da innerhalb solcher Immuntherapien schon ohne Strahlentherapien jahrelang anhaltende Vollremissionen möglich sind, wird unklar bleiben, ob sie nicht auch ohne Strahlentherapien hätten erzielt werden können. Im Falle eines solchen Therapieerfolges, den man keinem Patienten missgönnen würde, wäre die Zuordnung des Ergebnisses an das eine oder andere Verfahren im Nachhinein ohnehin nicht angebracht. Das Risiko besteht hingegen vielmehr darin, dass sich niemand mehr in der Radioonkologie Gedanken machen würde, wie er ohne die genannten medikamentösen Immuntherapeutika, deren Verwendung allein schon ein hohes tödliches Risiko beinhaltet, ganz gezielt und quasi risikolos ohne chronische Nebenwirkungen mit seinen Geräte-Ressourcen Abskopaleffekte verursachen könnte. Vorausgesetzt natürlich, ihm stünde ein Cyberknife, Gammaknife oder zumindest ein Stereotaxiezusatz für seinen Linearbeschleuniger zur Verfügung. Insofern bleibt die Radioonkologie gefordert, mit dem jetzigen Wissen solche Abskopaleffekte im Sinne von RASIs zu kreieren, weiterzuentwickeln und zu regelmäßig erzielbaren Resultaten zu vervollständigen – völlig losgelöst von medizinpolitischen oder gar ökonomischen Rücksichtnahmen gegenüber anderen medizinischen Fachgebieten oder gar gegenüber der Pharmazie selbst (und im besonderen Interesse unserer schwerkranken und nur noch palliativ behandelbar eingestuften metastasierten Krebspatienten). Nicht zuletzt ist immer wieder hervorzuheben, dass das bewusste Erzielen von Abskopaleffekten unter Anwendung von Hochdosistechniken der Radioonkologie mit weit weniger Risiken für den Patienten verbunden ist als die Anwendung von immuntherapeutischen Medikamenten.

Schlussfolgerungen

Radioonkologen sollten unter dem Eindruck aller drei Teile dieser Arbeit dafür Sorge tragen, beim Vorliegen mehrerer oder multipler Metastasen oder Tumore, unabhängig von der Pathohistologie, im Falle notwendiger oder evtl. auch nur möglicher Cyberknife-, Gammaknife- oder stereotaktischer Strahlentherapien die unter Vermeidung von Nebenwirkungen höchstmögliche Einzeldosis zu verabreichen, um abskopale Immuneffekte zu kreieren und eventuell mehrmals auszunutzen. Ersatz für höchste Einzeitdosen zwischen 19 und 23 Gy wären noch zweimalige Dosen von je ca. 15 Gy oder unter angeblich damit schon gesehenen Abskopaleffekten dreimalige Sitzungen mit jeweils 13 Gy, abhängig von den Bestrahlungsrisiken gegenüber dem direkten Umgebungsgewebe. Die Mindestgröße des Zielvolumens sollte bei 1,5 cm Minimaldurchmesser liegen, bei Abskopaltherapien inmitten von Tumorgewebe sollte das Zielvolumen einen

Durchmesser von mind. 2 bis 2,5 cm Durchmesser aufweisen. Tatsächlich erfolgreich ausgelöste Abskopaleffekte sollten anschließend genau dokumentiert, anonymisiert gesammelt und im Falle der Zustimmung durch die DEGRO (Deutsche Gesellschaft für Radioonkologie) an sie versandt werden, die dann die Synopse aus diesen Daten vornehmen und ergebnisoffen diskutieren und veröffentlichen könnte. Besonders interessant wäre es festzustellen, ob und in welchem (evtl. vermindertem Maße) Abskopaleffekte nach (lang anhaltenden) Chemotherapien überhaupt noch auftreten und wenn, dann unter welchen Immunitätsbedingungen (Maß der Unversehrtheit des lymphatischen Systems und seinen Untergruppen bzw. den Gleichgewichtsverhältnissen untereinander von B-, T-Lymphozyten, nat. Killerzellen, T-regulatorischen Zellen usw.). Auch wäre es sicherlich wichtig zu erfahren, ob und wann die neuen Therapien mit Antikörpern und Hemmstoffen das Generieren von Abskopaleffekten tatsächlich begünstigen oder deren Chancen vermindern würden. Sicherlich ist in jedem Einzelfall auch zu berücksichtigen, inwieweit tatsächlich Abskopaleffekte provoziert werden konnten bzw. ob sich solche Effekte im Rahmen von multimodalen Behandlungsformen überhaupt verifizieren lassen. Wichtig bleibt festzustellen, dass gerade auch in verzweifelten Situationen oftmals ohne wesentliche Risiken, da Normalgewebe hiervon nicht betroffen sind, Bestrahlungshöchstdosen direkt in Tumorgewebe eingestrahlt werden können, um zeitweise und wiederholbar Abskopaleffekte auszulösen und für Unbeteiligte

unerwartete klinische Remissionen zu erzeugen. Dann könnte die gezielte Provokation von Abskopaleffekten als neuartige Behandlungsmethode, als Abskopaltherapie unter Ersatz von ASIs durch RASIs in der Onkologie einen festen und noch deutlich ausbaufähigen Platz finden – in den meisten Fällen ohne Bevormundung durch Leitlinien, solange es denn die Therapie-Freiheit in Deutschland noch gibt. Widerstände hiergegen sind von konkurrierender, ökonomisch mitbetroffener Seite mit großer Sicherheit zu erwarten, obwohl oder gerade weil sich hierdurch mit gleich großer Sicherheit hohe Behandlungskosten, wahrscheinlich unter deutlich verringerten Nebenwirkungsrisiken und entsprechend verbesserter Lebensqualität betroffener Krebspatienten, einsparen ließen.

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Tumormarker in der Krebstherapie – Geschätzt oder unter Wert verkannt?

Teil I: Ein Statement aus der täglichen onkologischen Praxis
Teil II: Bedeutung von Tumormarkern für eine individuelle Behandlung von Krebspatienten, herausgestellt durch unterschiedliche Fallbeispiele

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Geschätzt oder unter Wert verkannt?

Teil I: Ein Statement aus der täglichen onkologischen Praxis Wulf-Peter Brockmann

Die nachfolgende Arbeit stellt zumindest im ersten Teil keine typische wissenschaftliche Abhandlung dar, sondern soll als Einleitung zu einem zweiten Teil mit praktischen Beispielen aus dem onkologischen Alltag vorrangig Denkanstöße vermitteln, die auf fast 40 Jahren eigener Beobachtungen und Erfahrungen innerhalb der diagnostischen und therapeutischen Onkologie beruhen.

In den Jahren von 1979 bis 1982 durfte der Autor regelmäßig wöchentlich einstündig an der Universitätsklinik Hamburg-Eppendorf sonographisch mit einem der ersten routinemäßig einsetzbaren Realtime-Ultraschallgeräte (Combison 100, Fa. Kretz-Technik) die Patienten der Pankreaskarzinom-Ambulanz des hauseigenen internistischen Gastroenterologen Prof. Dr. Rainer Klapdor in dessen Beisein diagnostisch betreuen. Abgesehen davon, dass aus dieser wertvollen Zusammenarbeit diverse Publikationen zur Sonographie in der Onkologie resultierten, erhielt der Autor permanent Einblick in die Tumormarker-Diagnostik bei Patienten mit gastrointestinalen Malignomen.

Prof. Klapdor hat seine Erkenntnisse zu diesem Thema nicht nur dem Autor dieses Artikels als damaligem Youngster der Radiologie weitervermittelt, sondern seit dem Jahr 1983 bis in die Gegenwart hinein in Hamburg ein internationales Symposium zur Tumormarker-Diagnostik ausgerichtet, an dem sich auch der Autor mit Ergebnissen seiner eigenen therapeutischen Möglichkeiten mehrmals beteiligen durfte.

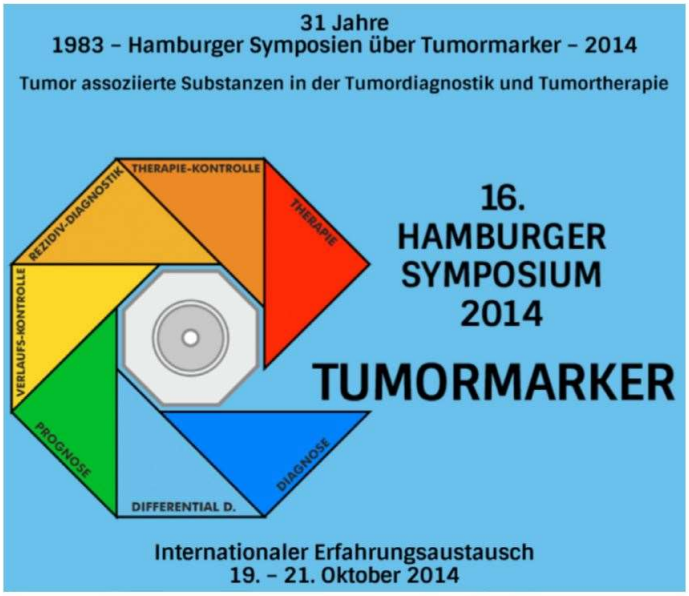

Abb. 1: Im Jahr 2014 feierte das Hamburger Symposium zur Tumormarker-Diagnostik sein bereits 31-jähriges Jubiläum

Serum-Tumormarker: Verkannt oder verbannt?

Obwohl als späterer Facharzt für Radiologie und Strahlentherapie in erster Linie an Schnittbildverfahren zur onkologischen Erst- und Verlaufsdiagnostik interessiert, musste der Autor immer wieder feststellen, dass zwar während seiner ersten Berufsjahre am UKE auch schon sehr kleine Tumor- oder Metastasenformationen sonographisch oder per Computertomographie detektiert werden konnten, dies aber immer wieder im direkten Zusammenhang mit

vorangegangenen Erhöhungen von Serum-Tumormarkertitern während akri bischer Serumkontrollen durch Prof. Klapdor.

Es sollte eigentlich jeden Kenner der Materie in Erstaunen versetzen, dass aus solchen Möglichkeiten in der Onkologie seit bald 40 Jahren zumindest in Deutschland keine weitergehenden Konsequenzen zum Nutzen der anvertrauten Krebspatienten gezogen wurden: Warum haben nicht einmal junge Kollegen den Wert einer Diagnostik erkannt (oder erkennen dürfen), die ihnen schon innerhalb weniger Wochen sehr eindeutig kundtun kann, ob sich ihre Behandlungen als erfolgreich erweisen oder als nutzlos aber risikoreich und mit schweren Nebenwirkungen behaftet?

Geht man erst einmal davon aus, dass junge Kollegen während ihrer Facharztausbildung noch ganz neutral und mit bestem Wissen und Gewissen an die Sache herangehen, so müsste man als Erklärung vermuten, dass sie vor der Tumormarker-Diagnostik schon deshalb zurückschrecken, weil ihnen während ihrer onkologischen Ausbildung immer nur die halbe Wahrheit vermittelt wurde, die eigentlich sogar nur aus kleinen Negativ-Bruchstücken besteht, während man den überragenden Wert der Methode ignoriert und verschweigt; wenn man nach dem Wert oder Unwert von Tumormarkern fragt, erhält man immer wieder die gleichen Antworten in folgender kleiner Auswahl (* = auf Kassenpraxen bezogen): · „Tumormarker bringen ja doch nichts. Die sind ja oft gar nicht erhöht." · „…die stimmen mit der Realität oft gar nicht überein." · „Positive Tumormarker findet man ja bei diesen Tumoren sowieso nie." · „Tumormarker-Untersuchungen sind viel zu teuer. Die sprengen mein Budget!" * · „Die darf ich ja gar nicht ausreichend oft kontrollieren. Dann sind sie doch sowieso nutzlos." *

14 wichtige Aspekte zu Serum-Tumormarkern

Bevor Kollegen auch zukünftig dank mitgeteilten Halbwissens oder infolge von Desinformationen auf Tumormarker, auf deren einschlägige Literatur oder gar auf Symposien zur Thematik lieber verzichten, sollten sie folgende Merksätze gelesen haben und deren Wahrheitsgehalt an möglichst vielen Patienten persönlich überprüft haben. Ihre zuvor ablehnende Haltung dürfte dann einem wachsenden Enthusiasmus gegenüber dieser wertvollen Unterstützung in Therapie und Diagnostik weichen:

1. Wichtig ist zu erfahren, ob prätherapeutisch, insbesondere präoperativ, positive Tumormarker vorliegen oder vorgelegen haben. Wenn ja, dann sollten sie postoperativ nach einigen Wochen in den Normbereich zurückfallen (möglichst bis ins untere Drittel). Bleiben sie erhöht, scheint postoperativ mindestens eine R1-Situation vorzuliegen oder sich eine Metastasierung zu entwickeln.
2. Wenn die Tumormarker – einmal normalisiert – über mehrere Wochen hinweg wieder ansteigen sollten (was anhand von drei Messungen in etwa zweiwöchigen Intervallen zu überprüfen ist), so muss mittels bildgebender Verfahren nach der Ursache und ihrer Lokalisation gefahndet werden, wobei sich insbesondere Schnittbildverfahren anbieten und unter diesen am ehesten das PET-CT als sicherste und in der Regel sensitivste Methode. Waren präoperativ mehrere Tumormarker positiv, braucht (aus Kostengründen) in aller Regel nur der stärker erhöhte Marker kontrolliert zu werden. Selten kommt es vor, dass einer der beiden angestiegenen Marker ein diskrepantes Verhalten gegenüber dem anderen erhöhten Marker aufweist. Dies wäre nur zu erwarten, wenn zwei unterschiedliche Zellklone unterschiedlich sensibel auf Therapien reagieren (mixed response), und jeder der beiden Klone einen eigenen Tumormarker exprimiert.
3. Ist eine onkologische Therapie (Chemoradiotherapie, Radiotherapie, Chemotherapie) besonders erfolgreich, sterben also in kürzester Zeit viele Tumorzellen, deren Inhalt bis ins Serum

gelangt, kann es anfänglich zu einem extremen Anstieg des Marker-Titers kommen, der dann jedoch schon innerhalb weniger Tage unter den Ausgangswert absinken sollte.

4. Steigt der Marker kontinuierlich in gleichem Maße an wie prätherapeutisch oder gar exponentiell, so ist von einem therapeutisch nicht beeinflussten Tumorprogress auszugehen und die Therapie zu wechseln. Bei sog. Immuntherapien mit Hemmstoffen oder Antikörpern kann diese Phase bis zum Absinken länger andauern; bei anderen antitumoralen Behandlungen sind jedoch Aussagen zur Erfolgstendenz oder zu einem unbeeinflussten Progress regelmäßig schon nach 2 – 3 Wochen möglich.
5. Der Normbereich ist für manche gebräuchliche Tumormarker (etwa CA 19-9, CA 125 und CA 15-3) sehr weit gefasst. Liegen für einen Patienten (wie dies in der Regel üblich ist) keine Tumormarker-Titer aus der Zeit vor der Erstdiagnose seines Malig noms vor, gilt im Falle eines sich einstellenden Behandlungserfolges das untere Drittel des Normbereichs als avisiertes Ziel.
6. Therapeutisch ist jedoch nicht nur ein Titer im unteren Normbereich anzustreben, sondern natürlich auch die Verhinderung eines Wiederanstiegs. Im Falle eines Wiederanstiegs spielt der Normbereich als solcher keine Rolle mehr. Das Ansteigen des Titers, also auch im Normbereich und innerhalb kurzer Zeit (innerhalb von 3 – 4 Wochen) über mind. 3 Kontrollen, ist stets alarmierend.
7. Wird ein Molekül / Eiweiß als Tumormarker einzig von einem ganz bestimmten Organ oder malignen Organtumor exprimiert, darf es eine gewisse Zeit nach operativer Entfernung des gesamten Organs / Tumors (z.B. Prostata-Karzinom) nicht mehr im Serum nachweisbar sein. Ein sog. PSA-Rezidiv ist dann immer (!) mit einem Tumorrezidiv gleichzusetzen, das so früh wie möglich eliminiert werden muss, um ein kuratives Behandlungsergebnis auch weiterhin anstreben zu können. Eine geringe Titerhöhe spricht dabei eher für ein lokales Rezidiv-Geschehen. Hohe Titer weisen auch auf ossäre oder lymphogene Fernmetastasen hin (→ Kontrolle durch PSMA-PET-CT).
8. Nicht jeder erhöhte Tumormarker spricht per se für das Vorliegen von Tumorzellen, nicht jeder Anstieg im Serum ist ein untrügliches Zeichen für einen (malignen) Tumor oder einen Tumorprogress: Manche Tumormarker können auch infolge von inflammatorischen Veränderungen unterschiedlichster Ätiologie / Genese vermehrt ins Serum exprimiert werden wie u.a. das CEA und das M2-PK. Das CEA kann darüber hinaus auch bei Rauchern erhöht sein. Ist der M2-PK-Titer zu hoch, sollte beispielsweise zum Ausschluss einer entzündlichen Darmalteration als Ursache auch das M2-PK im Stuhl gemessen werden, was im positiven Falle eine entzündlich intestinale Genese fast schon beweist. Bei negativem Stuhlbefund kann auch eine anderweitige bakterielle oder abakterielle Inflammation einen Tumorprogress mit erhöhtem M2-PK vortäuschen, insbesondere wenn zuvor tatsächlich eine erfolgreiche Malignomtherapie mit anschließend entsprechend fallenden Titern durchgeführt worden war.
9. Der Pathohistologie mancher Malignome, u. a. sogar abhängig vom Tumor-Grading, lassen sich häufiger als der Pathohistologie anderer Krebsformen ganz typische Tumormarker zuordnen: zur beispielhaften Veranschaulichung siehe Tabelle in Abbildung 2 aus einem Booklet über Tumormarker von Dr. med. Dirk Happich, FA für Laboratoriums- und Transfusionsmedizin, Leverkusen.1-4 Welcher Tumormarker als Verlaufsparameter für einen bestimmten Patienten und seine Erkrankung tatsächlich in Frage kommt, lässt sich prinzipiell nur probatorisch feststellen.
10. Die Menge des Markers im Serum korreliert zwar in gewissen Grenzen mit der Tumormasse im Körper, aber höchst unterschiedlich im interindividuellen Patientenvergleich. Im intraindividuellen Verlauf sagt dann die Steilheit des Markeranstiegs im Falle eines Progresses deutlich mehr über die Intensität des Tumorprogresses aus. Dramatisch zunehmende Marker-Titer bei vorheriger eher geringer Erhöhung müssen ans Einsetzen einer Metastasierung

denken lassen. Klinische Tumorstadien und quantitative Untersuchungsresultate zugehöriger Tumormarker korrelieren folglich nur in einer gewissen Bandbreite: aus dem Kontrollergebnis lässt sich im Einzelfall die Quantität der Tumormasse nur sehr bedingt ablesen. Diesbezüglich sind bildgebende Diagnostiken unumgänglich.

11. Ein drastischer Anstieg direkt nach Beginn einer neuen Therapie deutet in der Regel nicht auf einen Tumorprogress hin, sondern auf die umgehende Vernichtung einer großen Anzahl von Tumorzellen, deren Inhalt – also auch der Tumormarker – ins Serum fließt und dort kurzzeitig zu einem Peak führt, der ebenso schnell wieder abfällt (in aller Regel unter den Ausgangstiter).

12. Sind die typischen Tumormarker trotz makroskopisch eindeutig vorhandenem Tumorgewebe negativ getestet worden, sollte man noch weitere Tumormarker kontrollieren, da untypisch nicht gleich ausgeschlossen heißt (z. B. nach eigenen Erfahrungen des Autors das AFP beim malignen Pleuramesotheliom oder – bei aller Vorsicht – M2-PK beim Mamma-Ca, beim Papillen-Ca des Pankreas, beim Ovarial-Ca u. a.). Man denke als Ursache hierfür daran, dass Tumorzellen einer embryonalen Regression unterworfen sind und dabei letztlich jedes Eiweiß exprimieren können, dessen Synthesemöglichkeit im Genom festgeschrieben ist, obwohl diese Synthese, denkt man an das primäre Organ des Malignoms, eigentlich geblockt sein müsste.

13. Wirklich jede Verlaufskontrolle von Tumormarker-Titern sollte in einer Grafik zusammen mit den zuvor gefertigten als Diagramm dokumentiert werden, d. h. möglichst vom gleichen Labor, da die Normwerte von Labor zu Labor differieren können und kein Labor die Werte eines zuvor beauftragten kennen kann. Nur der Verlauf des Titers in einem solchen Diagramm kann auf den ersten Blick Aussagen über eine Therapie ermöglichen, insbesondere, wenn man in diese Diagramme die Termine der Behandlungsapplikationen einträgt. Dies wird im zweiten Teil der Veröffentlichung noch anschaulich dargestellt werden.

14. Die Kosten von Tumormarkerkontrollen stehen in keinem Verhältnis zu denen moderner, extrem teurer Hemmstoff- und Antikörpertherapien. Die Kostenersparnis der Krankenkassen schon bei einem einzigen Patienten infolge eines rechtzeitigen Absetzens dieser Medikamente bei Tumormarker-bedingter Detektion eines Erkrankungsprogresses sollten Anlass dazu geben, die Frequenz ihrer Abrechenbarkeit quartalsmäßig nicht mehr zu limitieren, sondern der Entscheidung onkologisch erfahrener Ärzte zu überlassen. Das Festhalten an gegenteiligen Überlegungen könnte als Votum zugunsten der Hersteller solcher Medikamente und zuungunsten der Versicherten gewertet werden.

Zusammenfassung mit Schlussfolgerungen

Geht man davon aus, dass ein früh erkanntes und umgehend beseitigtes Tumorrezidiv, lokal oder als singuläre oder Oligo-Metastasierung auftretend, die Heilungsrate erhöht oder zumindest die Gesamtüberlebenszeit und die Lebensqualität infolge längerer Zeiten ohne notwendige belastende therapeutische Maßnahmen steigert, dann ist hierfür der Einsatz von Tumormarkern unbedingt geboten – eigentlich eine Voraussetzung zum Erreichen hochgesteckter Behandlungsziele. Bildgebende Verfahren bei vorgefassten Nachsorgeterminen (etwa im Drei- oder Sechsmonatsintervall) können hierfür zu spät kommen und weisen zusätzlich methodisch bedingte eigene diagnostische Unsicherheiten wegen ihrer großen Anzahl möglicher Differenzialdiagnosen auf. Diese Vielfalt kann weitere Bilddiagnostiken mit vorherigen Terminierungsintervallen provozieren und damit auch einen weiteren, vermeidbaren Zeitverzug bis zum Einsetzen einer notwendigen Therapie oder Therapieänderung.

Geht man zusätzlich davon aus, dass fast jede lokale oder lokoregionäre Ausbreitung solider Malignome (Karzinome oder Sarkome) mit einer entsprechend lokalen oder lokoregionären Behandlung (operativ und /oder (chemo)radiotherapeutisch) gestoppt oder in einigen Fällen auch kurativ angegangen werden kann und damit (noch) keiner (eventuell extrem teuren und in aller Regel

Tumor/Region	Tumormarker	Empfohlene Kombination	Diagnose	Staging	Prognose	Monitoring
Tumore der Atemwege						
Bronchial-Ca						
kleinzelliges-Ca (SCLC)	NSE, ProGRP, PTHRP, CEA, TPA	NSE	+++			+++
nicht-kleinzelliges-Ca (NSCLC)	CYFRA 21-1	CYFRA 21-1	++	+	++	+++
Plattenepithel-Ca	CYFRA 21-1, CEA, SCCA	CYFRA 21-1, SCCA	++	+	++	+++
Adeno-Ca	CYFRA 21-1, CEA	CYFRA 21-1, CEA	+	+	++	+++
Gastrointestinale Tumore						
Magen-Ca	CA 72-4, CEA, CA 19-9	CA 72-4, CEA	+	+	++	+++
Ösophagus						
Plattenepithel und Adeno-Ca	CYFRA 21-1, CEA, SCCA	CYFRA 21-1, CEA, SCCA	+			++
Pankreas						
Adeno-Ca	CA 19-9, CEA, CA 125, CA 72-4	CA 19-9, CEA	++		+	+++
Gastrinom	Gastrin, Chromogranin A	Gastrin, Chromogranin A				
Insulinom	C-Peptid, Insulin, Chromogranin A	C-Peptid, Insulin, Chromogranin A				
Glucagonom	Glucagon, Chromogranin A	Glucagon, Chromogranin A				
Leber/Galle						
Leberzell-Ca	AFP, CEA, CA 19-9, HCV, HBV	AFP, CEA	++	+	+	+++
Gallengangs-Ca	CA 19-9, CEA, CA 125	CA 19-9, CEA	+		++	+++
Leber-Metastasen	CEA	CEA	++		++	+++
Kolon-Rektum-Ca	CEA, CA 19-9, Hb-/ Hb-Hpt, M2 PK, Calprotectin	CEA, CA 19-9, Hb-/Hb-Hpt im Stuhl	+++	+	++	+++
Anal-Ca	SCCA, CEA	SCCA, CEA				
Gynäkologische Tumore						
Mamma-Ca	CA 15-3, CEA, CA 125, HER2/neu	CA 15-3, CEA	+	++	+++	+++
Ovarial-Ca	CA 125, CA 72-4 (CA 15-3, CEA), HE4 Protein	CA 125, CA 72-4	++	++	++	+++
Keimzelltumore	AFP, ß-hCG	AFP, ß-hCG	+++	+	++	+++
Uterus-Ca						
Zervix-Ca	SCCA, HPV, CEA	SCCA, HPV	+	+	+	+++
Korpus-Ca	CA 125, CEA, CA 19-9	CA 125, CEA				
Blasenmole, Chorion-Ca	ß-HCG	ß-hCG	+++	+++	+	+++
Urologische Tumore						
Nieren-Ca	CEA, M2 PK, Erythropoetin, NSE, Renin, Ferritin, Neopterin		+			
Harnblasen-Ca	NMP 22, CYFRA21-1, SCCA, CEA, UroVysion FisH	NMP 22, CYFRA 21-1	++	+	+	++
Seminom, Teretrom	AFP, ß-hCG, PLAP, NSE	AFP, ß-hCG, (PLAP)	+	+	+	+++
Prostata-Ca	PSA, fPSA, cPSA, CEA	PSA, fPSA	+	+	+	+++
Keimzelltumore	AFP, ß-hCG	AFP, ß-hCG	+++	+	+++	+++
Tumore endokrines System						
Hypophysen-Tumoren	Prolaktin, ACTH, HGH, Cortisol, LH, FSH, TSH	Prolaktin, HGH, ACTH				
Schilddrüsen-Ca						
papillär/follikulär	Thyreoglobulin (HTG), CEA, NSE	HTG, CEA	+	+		+++
medullär	Calcitonin, CEA, NSE	Calcitonin, CEA	+++	++	++	+++
Nebenschilddrüsen-Ca	PTH	PTH				
NNR-Tumoren	Cortisol, DHEAS, Cortisol-Tagesprofil, Dexamethasontest	Cortisol, DHEAS	++	++	++	++
Phäochromozytom	Metanephrine, Katecholamine, Chromogranin A (Cg A), NSE	CgA, Katecholamine, Metanephrine	+++			+++
Neuroendokrine Tumore	Chromogranin A (CgA), NSE, Dopamin	CgA, NSE	++	++	++	+++
Karzinoid	5-HIES, Serotonin, Chromogranin A (Cg A), NSE	CgA, 5-HIES	++	++	++	+++
Neuroblastom	VMS, HVS, LDH, Chromogranin A (Cg A), NSE, Dopamin	VMS, HVS, LDH	++	++	++	++
Malignome lymphatisches und myeloisches System						
Allgemein	Thymidinkinase (TK), ß-2-Mikroglobulin (ß-2-MG), LDH, Ferritin	TK, ß-2-MG	+		+	+
Myelom/Plasmozytom	Immunfixation (monokl. Gammopathie, Bence-Jones-Paraproteine), freie Leichtketten (je Serum/Urin), Immunphänotypisierung	Immunfixation, freie Leichtketten	+++			+
Leukämie/Lymphome	Immunphänotypisierung, ZAP70, IgVH, Lymphozytendifferenzierung inkl. FISH- und molekularbiologische/ zytogenetische Diagnostik	Immunphänotypisierung				
MPN	JAK2	JAK2	++		++	
CML	BCR-Abl	BCR-Abl	++		++	
Verschiedene Tumore						
Melanom	Protein S-100, 5-Cysteinyldopa	Protein S-100	+	+++	+++	+++
Osteosarkom	Ostase, Hydroxyprolin, TPA, CEA, Osteocalcin	Ostase, Osteocalcin	++	+	+	++
Knochenmetastasen	Ostase, Desoxypyridinolin, Pyridinolin, Osteocalcin, Marker des Primär-Tumors	Pyridinolin im Urin, Desoxypyridinolin im Urin	++	++	++	++
+++ empfohlen	++ geeignet	+ eingeschränkt	nicht geeignet			

Abb. 2: Empfehlung und Wertigkeit von Tumormarkerkombinationen (aus: Happich D: Tumormarker in der Krebsdiagnostik. Labor Dr. Wisplinghoff)

nur palliativen) systemischen belastenden Therapie bedarf, so würde eine Ausweitung des Einsatzes von Serumtumormarkern zum richtigen Zeitpunkt mit Sicherheit einen systemischen pharmakoonkologischen Einsatz in vielen Fällen verzögern und den Patienten in einigen Fällen auch ganz ersparen, aber zumindest fakultativ die Überlebenszeit in annehmbarer Lebensqualität verlängern helfen.

Dass Tumormarker den Einsatz extrem hochpreisiger Medikamente in Fällen eines Tumorprogresses schon bei der Erstlinientherapie innerhalb kürzester Zeit ad absurdum führen können, aber ebenso auch den Einsatz von systemischen Zweit- oder Drittlinienbehandlungen, scheint man zu wenig zu berücksichtigen. Die vom Autor fast täglich zu erkennende Ablehnung von Tumormarkern bzw. die Ignoranz gegenüber ihren Möglichkeiten innerhalb von Therapieverläufen ist daher kaum oder allenfalls provokant zu erklären. Darüber hinaus lässt sich allzu oft in Anamnesen und schriftlichen Unterlagen von Krebspatienten sogar präoperativ eine Tumormarker-Diagnostik vermissen.

In Therapiestudien könnte sich andererseits unter kurzfristig regelmäßigen Kontrollen von anfänglich schon positiven Serumtumormarkern der Parameter Time-to-Progress drastisch verkürzen, und würde nicht mehr durch die Vorgabe mehrmonatiger bildgebender Kontrollintervalle gestreckt, was zur Einschränkung teuerster Medikamentenapplikationen führen könnte.

Die Verfestigung der bisherigen eher bedenklichen aber vermeidbaren Umstände dürfte auch auf den Vorgaben des Gemeinsamen Gebührenausschusses bezüglich der zu geringen Anzahl abrechnungsfähiger Untersuchungen unterschiedlicher Tumormarker pro Kassenquartal und der mäßigen abrechnungsfähigen KontrollFrequenz, bezogen auf einen einzelnen schon positiv getesteten Tumormarker (nur bis zu fünfmal pro Quartal), beruhen.

Die Stoßrichtung der Kritik

Der Wert dieser Marker wird anscheinend von den jüngeren Kollegen mangels Wissens und aufgrund von Halbinformationen bzw. gezielten Desinformationen nur verkannt. Diese Entschuldigung dürfte auf ältere Kollegen, die in onkologisch verantwortlicher Position tätig sind und eventuell erkannt haben, dass sich der unstrittige Wert von positiven Serum-Tumormarkern im Hinblick auf große Teile der Studienmedizin und Pharmakoonkologie als ökonomisch kontraproduktiv herausstellen könnte, kaum zutreffen, was auch onkologische Leitlinien in ein eigentümliches Licht rücken könnte. Besonders fragwürdig erscheint dem Autor die Rolle des GBA, der bei diesem Thema eine Vorreiterrolle zur Manifestierung einer Zweiklassenmedizin übernommen zu haben scheint, da er dafür gesorgt hat, dass momentan immer noch allein Privatpatienten und Selbstzahler bei negativer Kontrolle von zwei Standardtumormarkern durch die behandelnden Kollegen nach weiteren Tumormarkern im gleichen Quartal suchen lassen dürfen und anschließend von ausreichend engmaschigen Untersuchungen positiver Tumormarker quo ad vitam profitieren können.

Besagte Kritik am onkologischen Establishment trifft jedoch nicht weniger auf die Kollegen zu, die sich selbst zwar für onkologisch komplementär oder onkologisch alternativ tätig halten, aber sich einer viel zu geringen Anzahl therapeutischer Methoden bedienen – unabhängig von der zugrundeliegenden Pathohistologie und dem Grad der Malignomausbreitung lokal, lokoregionär oder metastatisch.

Je mehr Methoden man diesbezüglich beherrscht, desto nachvollziehbar relevanter werden Tumormarker-Verlaufstiter – hat man doch frühzeitig, d. h. zwar schon im Progress, aber noch ohne allzu große Massenzunahme von Tumorgewebe weitere Therapiemöglichkeiten zur Auswahl, den Titer-Anstieg umzukehren und eine Remission zu bewirken.

Wer innerhalb oder außerhalb von Leitlinien onkologisch tätig ist, aber kaum etwas von Tumormarkern hält, setzt sich somit zwangsläufig dem Verdacht aus, sich entweder unzureichend informiert zu haben oder nur möglichst lange an den wenigen Maßnahmen, die er beherrscht, oder die ihm (durch wen auch immer) vorgegeben zu sein scheinen, festhalten zu wollen. Früh erkannte, ansteigende Tumormarkertiter würden dabei wohl nur empfindlich stören. Einen solchen gemeinsamen kleinsten Nenner sollte in der Leitlinien- wie Komplementäronkologie jeder Kollege für sich persönlich vehement zurückweisen können.

Resümee

Der Tumormarkerverlauf ist eine weder von Skepsis noch Erfolgsdruck beeinflussbare neutrale Kennzeichnung des Erfolges oder Misserfolges einer Krebstherapie. Hieraus ergibt sich, dass akribisch terminierte und grafisch dokumentierte Verläufe von Tumormarkertitern möglicherweise jahrelange teure medizinische Studien verkürzen, wieder bezahlbar machen und aus bestimmtem Sichtwinkel sogar ersetzen: Eine Behandlung, die kontinuierlich oder schließlich exponentiell ansteigende Titer nicht verhindern kann, ist frustran und damit für den Patienten nutzlos. Eine Therapie, die schnell, also schon vor jeder bildgebenden Diagnostik ein kontinuierliches Absinken des Markertiters zur Folge hat, muss hingegen mit einer positiven Wirkung korrelieren. Geschieht dies bei bestimmten Behandlungen häufig, sehr häufig oder gar regelmäßig, könnte sich dies u.a. sogar als relevant für Sozialgerichtsverfahren zu Kostenübernahmen onkologischer Therapien erweisen, wenn es darum geht, ob sich strittige Behandlungsmethoden (als Ersatz für Leitlinienbehandlungen) als Erfolg versprechend erweisen (und sei dies nur durch Indizien belegt), falls aktuell noch keine jahrelang erhobenen / auszuwertenden Studienergebnisse zum Beleg ihrer Wirksamkeit vorlägen, die Aussagen zu den beiden ausschlaggebenden onkologischen Erfolgsparametern Time-to-Progress oder Überlebenszeit (-Verlängerung) erlauben würden.

Geht es nämlich sozialrechtlich nach dem dritten Kriterium des sog. Nikolausbeschlusses des BVerfG von 2005, eingearbeitet 2012 in das SGB-V, so stellen während einer Behandlungsmethode oder Methodenkombination regelmäßig über einen längeren Zeitraum hinweg sinkende Tumormarkertiter ausreichend justiziable Indizien für deren Wirksamkeit dar, insbesondere, wenn solche Verläufe wie beispielsweise im Rahmen von kapazitiven Radiofrequenz-Hyperthermieserien wiederholt oder regelmäßig auftreten – und dies unabhängig von der Art des Tumormarkers und unabhängig von den primären Pathohistologien der Erkrankten. Die Aussagen dieser Abhandlung in den Absätzen 1 – 14 werden in einem zweiten Teil durch eine umfangreiche Darstellung entsprechender Verläufe untermauert.

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Quellen und Literaturangaben finden Sie in Teil II.

Tumormarker in der Krebstherapie – Geschätzt oder unter Wert verkannt?

Teil I: Ein Statement aus der täglichen onkologischen Praxis

Teil II: Bedeutung von Tumormarkern für eine individuelle Behandlung von Krebspatienten, herausgestellt durch unterschiedliche Fallbeispiele Wulf-Peter Brockmann

Falls im ersten Teil der Arbeit noch nicht ausreichend betont worden sein sollte, dass weder der erste noch dieser nachfolgende Teil auf alle Aspekte der Tumormarker-Diagnostik eingehen kann, sei hier noch einmal besonders hervorgehoben, dass sich dieser Artikel im Wesentlichen auf den Wert der Marker während des Verlaufes klinisch schon manifester solider Krebstumor-Erkrankungen in Bezug auf onkologische Behandlungen beschränkt. Die Arbeit soll genau hierauf ausgerichtet sein, ohne zur Diskussion beizusteuern, ob sich Tumormarker zur Erstdiagnostik bzw. zum Screening von Krebserkrankungen eignen könnten. Dieser zweite Teil der Ausarbeitung soll vielmehr dazu ermutigen, sich bei onkologischen Therapien mithilfe von verschiedenen klinischen, laborchemischen und nicht zuletzt auch bilddiagnostischen Kriterien zu diagnostischen Ergebnissen und hieraus resultierenden Behandlungen durchzuringen, die die Prognose der individuell zu behandelnden Patienten ständig weiter zu verbessern suchen. Da können im Einzelfall dem onkologisch tätigen, therapeutisch und diagnostisch nicht festgefahrenen, sondern nach allen Seiten hin offenen Arzt Assoziationen an eigene Erlebnisse mit anderen Patienten, das Erinnern an frühere Erkrankungsverläufe unter bestimmten Behandlungen und klinischen Bedingungen mit den daraus über Jahre hinweg resultierenden Daten deutlich mehr helfen als ein bloßer Griff nach Lehrbüchern oder der Vergleich einer komplizierten aktuellen Situation mit standardisierten Ergebnissen aus wissenschaftlichen Studien.

Die fünf größten Irrtümer gegenüber Tumormarkern

Zugunsten der ausführlichen Falldarstellung möchte ich auf die pauschalisierte Kritik an Tumormarkern nur kursorisch eingehen, da ihr polemisches Kalkül endgültig offensichtlich wird, wenn man beide Artikel dieser Abhandlung gelesen hat. Den ersten Teil mit dem Thema „Ein Statement aus der täglichen onkologischen Praxis" können Sie kostenfrei in der Wissenschaftsredaktion des Forum Medizin Verlags anfordern (E-Mail: medwiss@forum-medizin.de).

„Tumormarker bringen nichts und sind oft nicht erhöht."

Tumormarker sind im weiteren klinischen Verlauf bei allen Patienten wertvoll, bei denen sie präoperativ erhöht waren. Insofern spielt eine mangelnde Titererhöhung bei anderen Patienten zu diesem Zeitpunkt keine wertmindernde Rolle. Außerdem sind sie in der Mehrzahl der Fälle, bei denen sie typischerweise als erhöht gelten, auch tatsächlich erhöht. Darüber hinaus gibt es weitere Marker im Serum oder Plasma, die zwar im Hinblick auf die Tumor-Pathohistologie nicht typischerweise erhöht sind, aber bei hartnäckiger Suche herausgefunden und dann für den Patienten genauso sinnvoll kontrolliert werden können wie ein typisch positiv detektierter Marker. Hierzu zählen das TPA oder das M2-PK (mit entzündungsbedingten Einschränkungen).

„Tumormarker stimmen mit der Realität häufig gar nicht überein."

Dass sich mit Tumormarkertitern leider nicht immer die Realität onkologischer Situationen abbilden lässt, ist bedingt durch die Vielschichtigkeit der begleitenden Gegebenheiten und gilt in der Medizin auch für viele andere diagnostische Maßnahmen.

Solche eigentlich allgemein bekannten und trotzdem nolens volens akzeptierten Einschränkungen in Bezug auf ihre Treffsicherheit mit Spezifität und Sensitivität beziehen sich eben nicht nur auf Tumormarker, da die Medizin (zum großen Bedauern des Autors) eben keine exakte Naturwissenschaft darstellt, sondern nur eine Kunde, also eine Wissenschaft auf empirischer Basis.

Trotzdem ist die Treffsicherheit von Tumormarkern bei sensiblem Umgang mit ihnen ausreichend hoch, um sie zum Nutzen von Krebspatienten und insbesondere unter Berücksichtigung weiterer Daten, insbesondere weiterer Laborwerte, sinnvoll einzusetzen.

„Positive Tumormarker findet man doch bei diesen speziellen Tumoren sowieso nie. Warum also suchen?"

Zwar findet man positive Tumormarker bei manchen Tumoren selten; aber auszuschließen sind sie niemals so kategorisch, wie man dies leider immer wieder glauben machen möchte. Mag die Vergeblichkeit dieser Suche auf manche Tumor-Pathohistologien sogar recht regelmäßig zutreffen, spielt dies jedoch bei der Mehrheit der Pathohistologien von Krebstumoren keine Rolle, da es für die überwiegende Anzahl solider Krebsformen eben doch positive Marker oder Ersatzmarker (M2-PK) gibt, wenn man nur ausreichend lange sucht. Dass es selbstverständlich immer wieder einzelne Patienten gibt, die gar keine positiven Tumormarker aufweisen – d. h. auch schon präoperativ nicht – schmälert den Wert solcher Marker nicht grundsätzlich und sollte niemanden entmutigen: Es finden sich auch bei Karzinomerkrankungen ohne typische Tumormarker immer noch viele Patienten, für die sich eine weitergehende Suche lohnt. Anhand der letztlich dann doch noch gefundenen Marker kann die Evidenz von Therapieerfolgen oder -misserfolgen zum Wohle der Patienten häufiger und schneller kontrolliert werden, als dies per Schnittbildverfahren möglich wäre.

„Tumormarker-Untersuchungen sind viel zu teuer. Die sprengen das Budget meiner Praxis und sind wirtschaftlich nicht vertretbar!"

und

„Tumormarker darf ich ja gar nicht ausreichend oft kontrollieren. Und ohne regelmäßige Kontrollen sind sie doch eh nutzlos."

Die beiden Aussagen, Tumormarker-Untersuchungen seien viel zu teuer und sprengten daher das Budget der Überweiser, und man dürfte Tumormarker gar nicht ausreichend häufig kontrollieren, weshalb sie ohnehin nutzlos wären, sind typische und weit verbreitete, vielleicht gar gezielt in Umlauf gebrachte Halbwahrheiten: Im Hinblick auf die Kosten aktueller und unzweifelhaft wertvoller Immuntherapien mit Antikörpern und Hemmstoffen von Tausenden Euro monatlich entsprechen die Kosten von SerumTumormarker-Kontrollen nicht einmal dem berühmten Tropfen auf dem heißen Stein. Ob sie ein Kassenarztbudget sprengen und wie häufig sie pro Quartal gegenüber den Gesetzlichen Krankenkassen abrechnungsfähig sind, sagt überhaupt nichts über ihren Wert an sich aus, sondern gibt allenfalls Raum für kritische Gedanken, die den Gemeinsamen Bundesausschuss für Ärzte und Krankenkassen (GBA) betreffen, der diesen Irrglauben mit solchen Forderungen und Ergebnissen seiner Politik selbst herbeigeführt hat bzw. immer noch fördert. Käme man den Forderungen des GBA nach Limitierung ihres Einsatzes stringent nach und würden sich daher bei Kassenpatienten sinnvolle Tumormarker-Kontrollen tatsächlich verbieten, entstünden gleichzeitig extrem hohe und eventuell unnötige onkologische Pharmaziekosten, falls deren teuerste Medikamente schon seit Wochen nicht mehr die erhoffte Wirkung erzielten.

Wäre es nicht eine mindestens ebenso einzufordernde Aufgabe des Gemeinsamen Bundesausschusses, letztgenannten Missstand zu beheben? Wäre der einzige Beweggrund des GBA, eine sinnvolle Tumormarker-Diagnostik bis in die Sinnlosigkeit hinein auszudünnen, tatsächlich nur die Ausschöpfung eines Einsparpotenzials, würde er sich insofern selbst konterkarieren. Es fällt einem unbefangenen Beobachter schon ein wenig schwer, sich dagegen zu wehren, so unökonomisch gedeckelte finanzielle Ressourcen unseres Gesundheitswesens einseitig und gleichzeitig nicht ganz unbeabsichtigt in Richtung Pharmazie kanalisiert zu sehen.

Die Fallbeispiele im Einzelnen

Fall 1 – Beispiel für eine mehrfache, rechtzeitige Bilddiagnostik mit umgehender, allein schon lokal ausreichender Therapie dank der Beachtung minimaler Tumormarker-Titererhöhungen, die sich innerhalb des Normbereiches vollzogen, sowie für einen diskrepanten Tumormarkerverlauf während des zuletzt nicht mehr zu stoppenden Metastasierungsprogresses.

Daten: L.-S., U., geb. 12/70, verst. 06/17.

Z.n. Mammakarzinom-OP re., triple neg., ohne adjuvante Maßnahmen (Pat.Ablehnung) mit BET 02/14

Die Erstvorstellung erfolgte 06/14 mit der Frage nach einer individuellen adjuvanten Therapie nach Mamma-Ca. 08/14 dann neuerliche Vorstellung, jetzt aber mit einem tastbaren riesigen lokalen axillären Tumorrezidiv rechtsseitig (Durchmesser > 13 cm). Die Patientin lehnte kategorisch jede Form einer systemischen Chemotherapie ab. Die anschließende weiterführende Schnittbilddiagnostik (MRTUntersuchung mit KM-Gabe i. v., prätherapeutisch im September 2014 und postradiotherapeutisch im Oktober 2014) sowie der weitere klinische Verlauf bis etwa August 2016 (in hervorragender, praktisch uneingeschränkter Lebensqualität ohne lästige Therapienebenwirkungen) geht aus den nachfolgenden kursorischen Tabellen genauso hervor wie die für diese Publikation wichtige enge Korrelation der beiden positiven Serumtumormarker CA 125 und CA 15-3 mit den zugrunde liegenden vielfältigen Behandlungen sowie den jeweils zuvor angefertigten Bildgebungen.

Erst ab etwa Ende September / Anfang Oktober 2016 kam es zu einer klinischen Verschlechterung mit zuletzt neuerlicher Lebermetastasierung und zuvor solitärer Pankreaskopfmetastase. Fachärztlicherseits wurden weitere Strahlentherapiemaßnahmen und ein palliativ operatives Vorgehen ebenso abgelehnt wie (weiterhin seitens der Patientin) eine systemische Chemotherapie; Ausnahme: Lowdose-Behandlungen in Kombination mit lokoregionären Elektrohyperthermien.

Es fanden jedoch zwischen Oktober 2016 und Januar 2017 noch drei auswärtige gezielte Chemoembolisationen der Leber ohne ausreichende Miteinbeziehung der Pankreaskopfmetastase und ohne Berücksichtigung der vorliegenden Chemosensitivitätstestung statt. Hierunter kam es allerdings nach der dritten Perfusion mit Chemotherapie-bedingten akuten Nebenwirkungen zu persistierenden Kortison-assoziierten ubiquitären Muskelparesen, insbesondere auch beider Arme und Beine aufgrund einer angeborenen Myopathie mit absoluter Minderung der Lebensqualität der Patientin. Weitere Therapiemöglichkeiten gegenüber einer nun auch noch aufgetretenen Lungenmetastasierung und knöchernen Metastasen, unter anderem an der Schädelbasis, zusammen mit der jetzt stark ausgeprägt progredienten Lebermetastasierung bestanden daher nicht mehr. Die Patientin verstarb im Juni 2017.

Bezüglich des Tumorprogresses muss wohl von einem besonders malignisierten Zellklon als auslösendem Moment einer zunehmenden Therapieresistenz ausgegangen werden, der sich von den übrigen Tumorzellen insoweit unterschied, als seine Exprimierung von Ca 15-3 ständig zunahm, während der Ca 125-Titer des übrigen Tumorgeschehens noch überraschend lange relativ konstant blieb (s. Abb. 1).

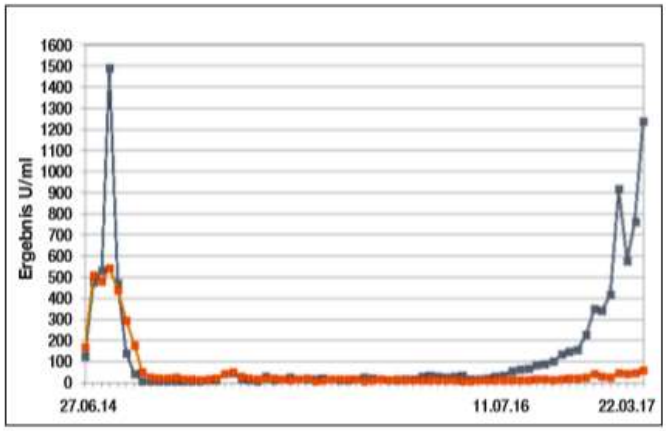


Abb. 1: Zuletzt stark diskrepanter Tumormarkerverlauf betreffend Ca 125 (graue Linie) und Ca 15-3 (orange Linie) zwischen 07/16 und 03/17

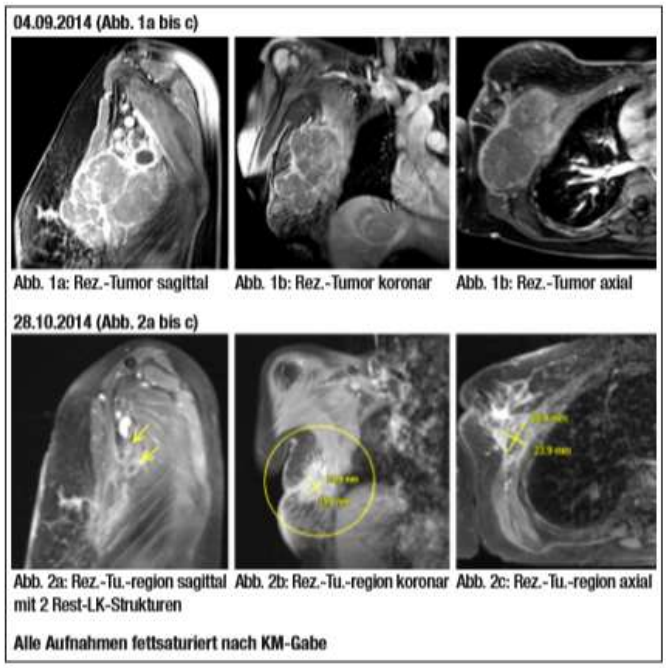


Abb. 2: MRT-Befund des axillären Mamma-Tumorrezidivs prä- und posttherapeutisch (Behandlung: hyperfraktioniert-akzelerierte Photonentherapie in Kombination mit Lowdose-Chemotherapie und simultaner Elektrohyperthermie)

27.06.14	Ca 125:	127,0 U/l	Ca 15-3:	170,0 U/l	auswärtiger Wert vor Therapiebeginn
12.08.14	Ca 125:	475,0 U/l	Ca 15-3:	508,0 U/l	MRT 04.09.14: Progress axillär → →
22.09.14	Ca 125:	470,0 U/l	Ca 15-3:	439,0 U/l	Radiatio * 09. – 10./14 + 3 Chemoperfusionen: 21.08., 06.11., 04.12.14
29.10.14	Ca 125:	9,6 U/l	Ca 15-3:	49,6 U/l	MRT 28.10.14: sehr gute Teilremission
12.01.15	Ca 125:	10,2 U/l	Ca 15-3:	17,4 U/l	PET-CT „ob" → 04/15 3 DC-Therapie-Impfungen 02. – 04./15
25.05.15	Ca 125:	40,8 U/l	Ca 15-3:	40,8 U/l	PET-CT: 2 Lungen-Metastasen 06/15 → Radiatio * 06/15
20.07.15	Ca 125:	17,0 U/l	Ca 15-3:	29,9 U/l	→ im Thorax-CT fast Vollremission
18.08.15	Ca 125:	9,4 U/l	Ca 15-3:	15,1 U/l	
07.09.15	Ca 125:	29,5 U/l	Ca 15-3:	20,8 U/l	PET-CT: 1 mediast. Metastase 06/15 → Radiatio * 06/15
12.10.15	Ca 125:	12,1 U/l	Ca 15-3:	19,9 U/l	erneute Remission (Tumormarker)
03.11.15	Ca 125:	15,5 U/l	Ca 15-3:	18,1 U/l	* jede Radiatio als Chemo-Radioth. (Metavect.-Analyse)
17.11.15	Ca 125:	*24,3 U/l	Ca 15-3:	10,5 U/l	+ 3 Chemoperfusionen: 12.11.15, 10.12.15 u. 14.01.16
23.12.15	Ca 125:	15,4 U/l	Ca 15-3:	15,1 U/l	– * wohl Chemoperfusions-bedingter Ca 125 Anstieg wegen Peritonealreizung beim abdominalen Perfusionsteil
28.12.15	Ca 125:	11,5 U/l	Ca 15-3:	15,4 U/l	
04.01.16	Ca 125:	12,2 U/l	Ca 15-3:	16,9 U/l	
18.01.16	Ca 125:	*26,0 U/l	Ca 15-3:	9,9 U/l	Vollremission angestrebt:
25.01.16	Ca 125:	*19,1 U/l	Ca 15-3:	12,8 U/l	→ 3 x Fiebertherapie
01.02.16	Ca 125:	18,5 U/l	Ca 15-3:	15,1 U/l	Feb. bis März 2016
15.02.16	Ca 125:	14,1 U/l	Ca 15-3:	14,4 U/l	
29.02.16	Ca 125:	13,9 U/l	Ca 15-3:	15,7 U/l	aber:
14.03.16	Ca 125:	16,6 U/l	Ca 15-3:	13,6 U/l	Tumormarkerverlauf nicht so wie erhofft
29.03.16	Ca 125:	16,8 U/l	Ca 15-3:	10,7 U/l	
19.04.16	Ca 125:	27,5 U/l	Ca 15-3:	13,8 U/l	
25.04.16	Ca 125:	34,5 U/l	Ca 15-3:	13,4 U/l	PET-CT mit solitärer Lu.-Metastase re. UL
02.05.16	Ca 125:	31,2 U/l	Ca 15-3:	11,5 U/l	und solitärer Leb.-Metastase Segm. V
11.05.16	Ca 125:	*25,6 U/l	Ca 15-3:	11,4 U/l	– Cyberknifetherapie + Organbestrahlg.
19.05.16	Ca 125:	*28,0 U/l	Ca 15-3:	10,9 U/l	plus EHY* u. LDC*
13.06.16	Ca 125:	*34,9 U/l	Ca 15-3:	9,6 U/l	– * länger persistierend wohl gegen Peritonal-
27.06.16	Ca 125:	15,0 U/l	Ca 15-3:	9,5 U/l	reizung aufgrund Ganzleberradiatio
04.07.16	Ca 125:	16,2 U/l	Ca 15-3:	12,0 U/l	
11.07.16	Ca 125:	19,5 U/l	Ca 15-3:	10,7 U/l	
26.07.16	Ca 125:	27,3 U/l	Ca 15-3:	12,0 U/l	
01.08.16	Ca 125:	35,0 U/l	Ca 15-3:	13,5 U/l	PET-CT mit solitärer LK.-Metastase am
22.08.16	Ca 125:	53,2 U/l	Ca 15-3:	14,1 U/l	Pankreaskopf wegen Vorbestrahlung
29.08.16	Ca 125:	62,1 U/l	Ca 15-3:	12,7 U/l	keine weitere Radiatio möglich →
05.09.16	Ca 125:	65,8 U/l	Ca 15-3:	13,6 U/l	Vorstellung zu OP und Darmverlagerung,
04.10.16	Ca 125:	133 U/l	Ca 15-3:	16,1 U/l	chirurgischerseite abgelehnt; →
31.10.16	Ca 125:	155 U/l	Ca 15-3:	19,5 U/l	Frankfurt (10/17 u. 11/17 u. 01/18) mit
09.11.16	Ca 125:	225 U/l	Ca 15-3:	23,6 U/l	arteriellen Leber-Chemoperfusionen *
02.12.16	Ca 125:	349 U/l	Ca 15-3:	40,4 U/l	mit kurzzeitigen Senkungen des Ca 15-3
02.01.17	Ca 125:	341 U/l	Ca 15-3:	31,2 U/l	bei unaufhaltsamen Anstieg des Ca 125
16.01.17	Ca 125:	416 U/l	Ca 15-3:	23,7 U/l	und Zunahme der Lebermetastasierung,
30.01.17	Ca 125:	915 U/l	Ca 15-3:	46,9 U/l	neu aufgetretenen Lungenfiliae und
24.02.17	Ca 125:	576 U/l	Ca 15-3:	42,7 U/l	ossären Metastasen bis zum
22.03.17	Ca 125:	761 U/l	Ca 15-3:	46,8 U/l	Tode der Pat. 06/17
22.03.17	Ca 125:	1.235 U/l	Ca 15-3:	56,8 U/l	* ohne Stopflow, ohne abdominale Oxygenierung, ohne simultane Hyperthermie u. ohne Chemorefiltration im Gegensatz zu denen in 08/14, 11/14 u. 12/14 sowie 11/15, 12/15 u. 01/16

Abb. 3: Korrelation zwischen Therapieerfolg und -misserfolg unterschiedlichster individueller antitumoraler Behandlungen und den beiden positiven Serumtumormarkern Ca 125 und Ca 15-3. ***Legende:*** *LDC = Lowdose-Chemotherapie, DC-Impfungen = Impfungen mit Dendritischen Zellen (GMP-Zubereitung unter Verantwortung des Autors im Reinraumlabor in Duderstadt). Die ersten 6 Chemoperfusionen (3× in 2014 und 3× in 2015/2016) als ORCP´s im Helios-Hanseklinikum, Stralsund (unter anderem die Abteilung für Gefäßchirurgie), gemäß „Liquid Biopsy"-Chemosensitivitätstestung, Institut Metavectum, Hamburg; die letzten drei in der Universitätsklinik Frankfurt (Abt. Intervent. Radiologie)*

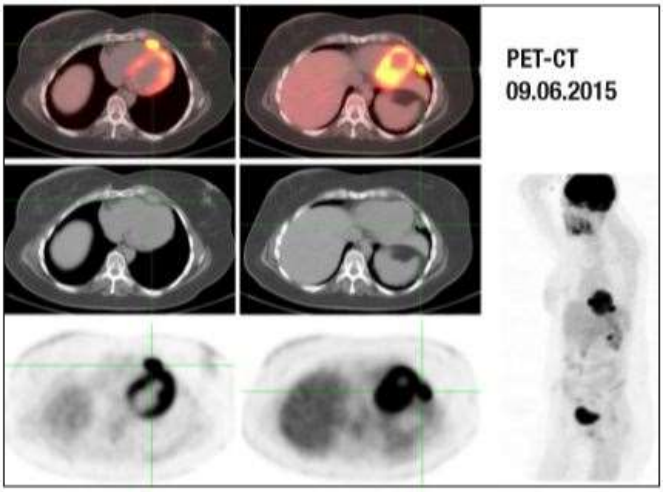


Abb. 4: PET-CT-Korrelation mit erstem Tumormarkeranstieg (noch im Normbereich) mit einer kleinen Metastase präkardial und intrathorakal epiphrenisch, beide umgehend per Cyberknife dauerhaft beseitigt.

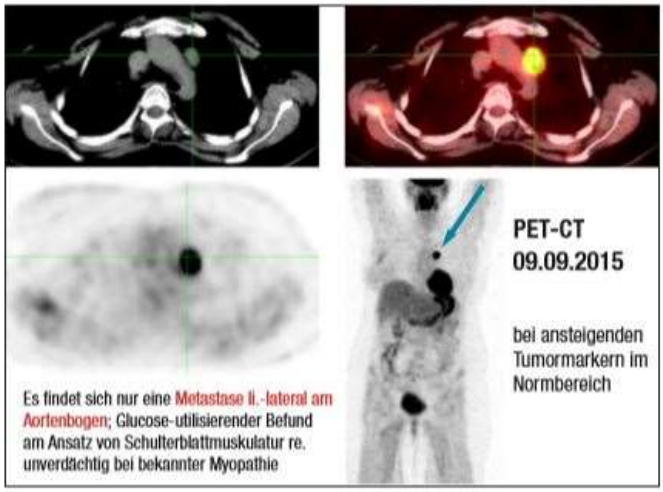
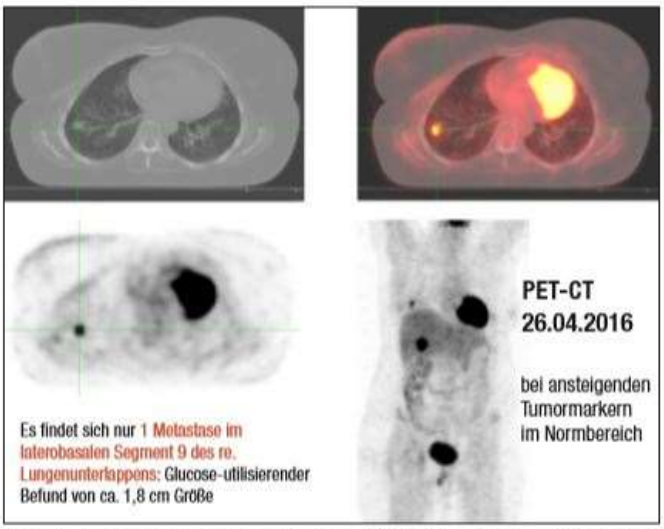


Abb. 5: PET-CT-Korrelation mit zweitem Tumormarkeranstieg (ebenfalls noch im Normbereich) mit einer mediastinalen Metastase am Aortenbogen, umgehend per Cyberknife dauerhaft beseitigt



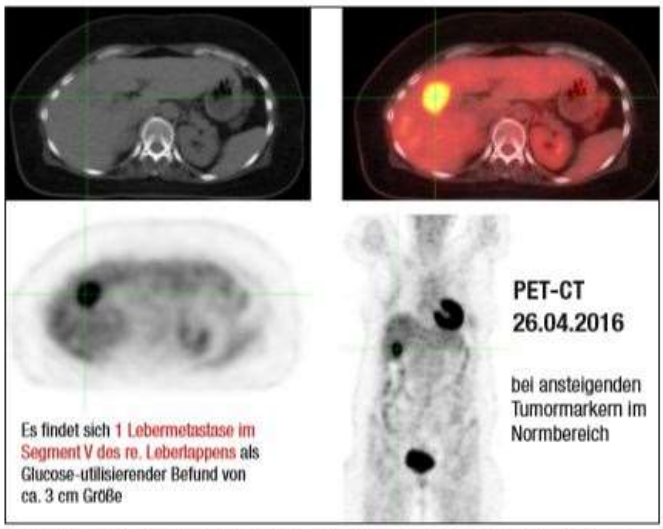


Abb. 6a und 6b: PET-CT-Korrelation mit drittem Tumormarkeranstieg (wiederum noch innerhalb des Normbereichs), mit einer einzelnen Lungenmetastase und einem einzelnen Leberherd, beide umgehend per Cyberknife dauerhaft beseitigt. Eine spätere neue Lungen- und Lebermetastasierung nahm nicht von diesen beiden Bereichen ihren Ausgang. Dabei ist hervorzuheben, dass nur geringe Titererhöhungen im unteren/mittleren Normbereich insbesondere des regelmäßig kontrollierten Ca 15-3 umgehend FDG-PET-CT's veranlassen ließen, und die so detektierten oligometastatischen Befunde ohne Zeitverzug Cyberknife-Behandlungen zur Folge hatten, was sicherlich den bemerkenswert langen klinischen Verlauf in praktisch uneingeschränkter Lebensqualität über zweieinhalb Jahre hinweg erst ermöglicht haben dürfte.

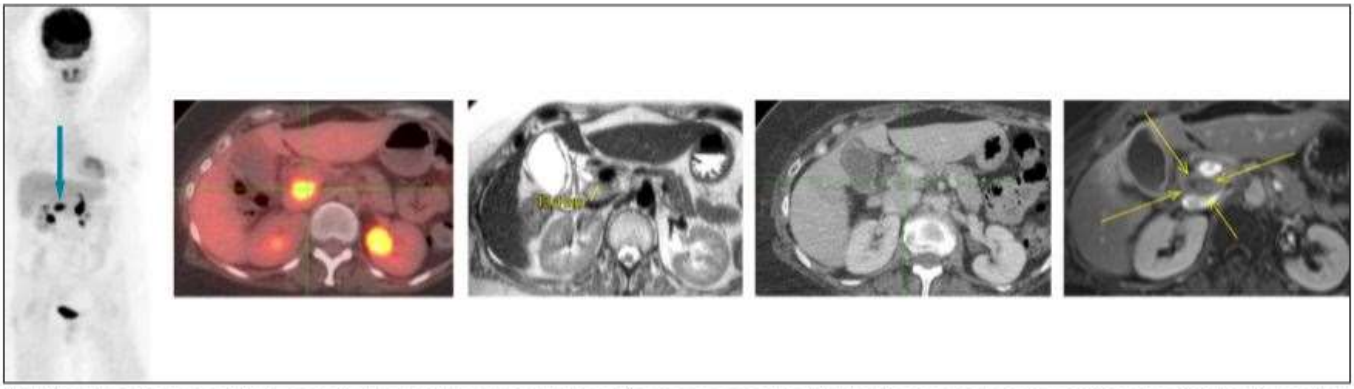


Abb. 6c: Neu aufgetretener Pankreaskopfbefund, nicht mehr lokal behandelbar wegen vorheriger Strahlentherapien und daraus resultierender etwaiger Dosisspitzen

Fall 2 – Beispiel für (Darm-)Infekt-bedingte M2-PK-Titererhöhung bei Mamma-Karzinom-Patientin kurz nach adjuvanter Tumortherapie.

Daten: H.S., geb. 06/80

Z.n. BET 05/2016 bei bifokalem, gut differenziertem Mammakarzinom li. (T1b, N0, M0, L0, V0, Er+, Pr+, Her-)

Die Tumormarker Ca 15-3 und Ca 125 wurden präoperativ nicht getestet und waren postoperativ vor adjuvanter Behandlung negativ. M2-PK als möglicher Ersatztumormarker im Vollblut wurd erstmalig direkt nach adjuvanter Strahlentherapie geringfügig positiv dokumentiert (23,9 U/ml), eventuell aufgrund einer lokalen radiogenen Reizsituation.

Die Therapie bestand aus einer hyperfraktioniert-akzelerierten Nachbestrahlung der linken Brust unter Lowdose-Chemotherapie gemäß Metavectum-Chemosensitivitätsanalyse im Sinne einer Liquid Biopsy (molekularbiologisch/molekulargenetisch dank Serum-Rückstellmuster nachprüfbar determiniert). Nach Therapieende unternahm die Patientin eine Studienreise nach Nepal. Anschließende M2-PKTiter-Erhöhung: 50,9 U/l. Positive M2-PK-Kontrolle im Stuhl; insofern keine Tumor-/Metastasen-bedingte M2-PK-Erhöhung im Plasma, sondern intestinal-infektiös bedingt im Rahmen des fernöstlichen Auslandsaufenthalts. Nach antibiotischer Behandlung negative Stuhlprobe und entsprechendes Absinken des M2-PK-Titers bei negativer FDG-PET-CT-Untersuchung. Bislang weiterhin unauffällige Nachsorge-Untersuchungen. Statt systemischer medikamentöser adjuvanter Maßnahmen (Ablehnung auch antihormoneller Behandlungen seitens der Patientin) nur unregelmäßige moderate Ganzkörper-Hyperthermien zur Verbesserung der zellulären Immunlage.

Datum	M2-PK-Titer im Plasma
18.01.17	23,9
01.02.17	50,9
13.02.17	19,7
23.03.17	11,8
17.10.17	5,5
01.02.18	8,3
28.05.18	12,4
01.08.18	14,8
26.10.18	10,3

Abb. 7a: M2-PK Plasmatiter-Verlauf in Zahlen

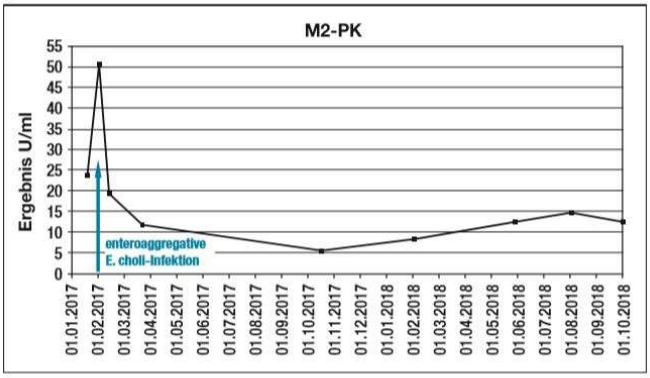


Abb. 7b: M2-PK Plasmatiter-Verlauf als Diagramm

Fall 3 – Beispiel für größtenteils Lymphom-bedingte M2-PK-Titer-Erhöhung vor Thera pie beginn mit oberer Abschnittsbestrahlung (erste Serie), nach Strah lentherapie der zwei ten Serie (untere Abschnittsbestrahlung) stark rückläufig.

Daten: P.C., geb. 03/88, M. Hodgkin, Std. IIIa, mit B-Symptomatik und großen, teils konfluierenden* Lymphknotenpaketen re.-zervikal, mediastinal* und subphrenisch paraaortal

Nachdem der Patient seinen schon bekannten M. Hodgkin re.- zervikal mehrere Jahre lang nur mit Vitamin C und vergleichbaren Maßnahmen hatte auswärtig behandeln lassen, lehnte er weiterhin Volldosis-Chemotherapien kategorisch ab, akzeptierte aber folgende individuelle Behandlungskombination nach Durchführung eines positiven PET-CT´s mit hyperfraktioniert-akzelerierter

Strahlentherapie des oberen Körperabschnitts (supraphrenisch), kombiniert mit Elektro hyperthermie und Insulin-potenzierter Chemo therapie, sowie anschließender unterer Abschnittsbestrahlung in gleicher Behandlungskombination: hierunter Abfall des M2PK-Titers von vor Beginn des zweiten Therapieteils (ca. 220 U/ml) auf knapp über 20 U/ml bei Strahlentherapieende. Patient bleibt unter radiologischer / radio onkologischer Nachsorge-Kontrolle.

Datum	Ergebnis U/ml
21.01.19	220,5
04.02.19	58,9
26.02.19	31,4
18.03.19	21,0

Abb. 8a: M2-PK Plasmatiter-Verlauf in Zahlen

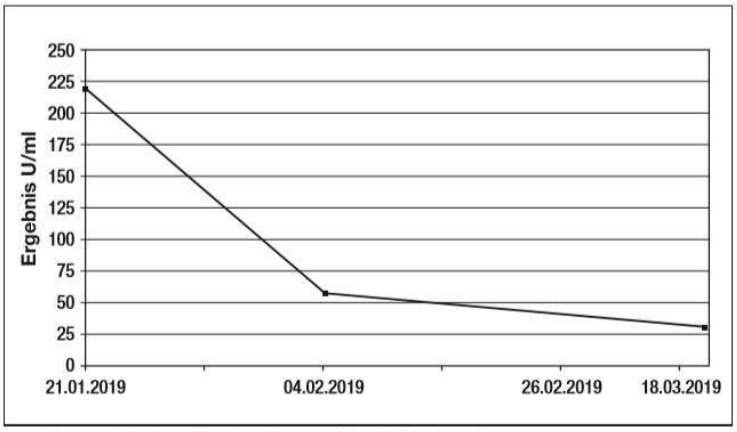


Abb. 8b: M2-PK, zeitlicher Plasmatiter-Verlauf als Diagramm

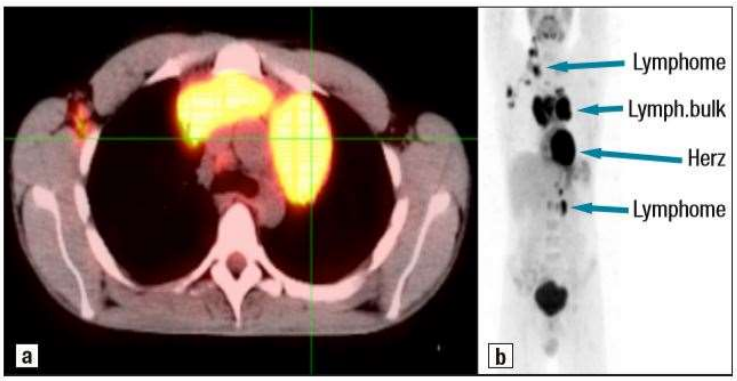


Abb. 9a (CT), 9b (PET): Mediastinaler Lymphom-Bulk

Fall 4 – Beispiel für Tumormarker-kontrollierte, erfolgreiche Langzeittherapie bei jungem Palliativpatienten mit Lebermetastasen und paraaortaler Bulk-Metastasierung mit letztlich wieder möglicher operativer R0-Resektion (retroperitoneal und hepatisch) und entsprechender Therapieziel- bzw. Prognoseänderung (palliativ → fakultativ kurativ)

Daten: B.E., geb. 06/91

Z.n. Hoden-Ca (Keimdrüsentumor) mit Bulk-Metastase retroperitoneal

re.-paraaortal.

Unter Volldosis-Chemotherapie erfolgte von Januar bis März 2018 (in Rumänien) nur eine zögerliche Verkleinerung einer großen retroperitonealen Metastase (> 18 cm auf etwa 8 cm) bei Vena cavaThrombose und Auftreten mehrerer Le ber metastasen. Die folgende Therapie (durchgeführt in Hamburg) bestand aus hyperfraktioniertakzelerierter Lowdose-Ganzleber-Photonenbestrahlung plus hyperfraktioniert-akzeleriertem Photonenboost der Retroperitonealmetastase, simultan und postradiotherapeutisch kombiniert mit Insulin-potenzierter Lowdose-Chemotherapie und Elektrohyperthermie. Dies führte zu einem Absinken des Tumormarkertiters AFP bis in den Normbereich. Daraufhin erfolgte eine operative Lebermetastasenentfernung und Resektion des retroperitonealen makroskopischen „Tumorrestes" unter teilweisem Vena cava-Ersatz.

Pathohistologische Tumorzellfreiheit in allen Präparaten, auch in der Leber, bewies das hervorragende präoperativ erzielte Ergebnis.

Datum	Ergebnis
27.02.18	27,9
05.03.18	27,6
27.03.18	22
30.04.18	16,4
06.06.18	14,4
19.06.18	13,1
19.07.18	10,1
07.08.18	9,8
21.08.18	10
10.09.18	9,4
09.10.18	6,8
21.11.18	8,8
28.01.19	5,3
05.02.19	5,3

Abb. 10a: AFP-Serumtiter-Verlauf ab hiesigem Therapiebeginn (Hamburg) 02/18 bis zur Metastasenresektion 02/19 in Zahlen

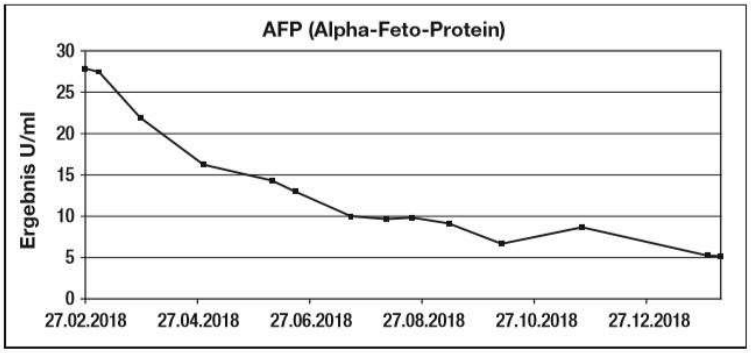


Abb. 10b: Zeitlicher Verlauf des AFP-Serumtiters zwischen hiesigem Therapiebeginn in 02/18 bis zur OP 02/19 als Diagramm

Fall 5 – Beispiel einer allein inflammatorisch induzierten M2-PK-Plasmaerhöhung bei einem Patienten mit Z.n. GIST-R0-Resektion in Magenregion.

Daten: W.S., geb. 01/70

Z.n. laparoskopischer Magenteilresektion wegen GIST (GastroIntestinaler Stroma-Tumor, 6,5 cm im Durchmesser) in 11/17; Relaparotomie 06/18 wegen Tumorrezidiv-Verdachts im PET-CT, operativ nicht bestätigt.

Nach Praxis-Erstvorstellung 09/18 und blande erhöhtem M2-PKTiter zeigte sich nachfolgend eine deutlichere Erhöhung und es folgte ein nochmaliges PET-CT (10/18) mit hochgradigem Verdacht

auf Lungenmetastasierung linksseitig. Nachts erfolgte, kurz vor dem jüngsten PET-CT, bei Refluxösophagitis infolge großer Magenhernie ein Vomitus im Schlaf, und es bestand Verdacht auf Aspiration in der Genese einer direkt nachfolgenden Pneumonie mit stundenlangem Hustenreiz. Es folgte eine erfolgreiche, zweiwöchige antiinflammatorische Behandlung mit Ezrin (Gepon®).

In zwei kurzen darauf nachfolgenden Kontroll-CTs (durchgeführt 11/18 und 03/19) zeigten sich unauffällige Lungenbefunde und parallel ein Absinken des M2-PK-Titers, jedoch (noch) nicht bis in den Normbereich, am ehesten wegen der persistierenden Refluxösophagitis.

Datum	Ergebnis
31.08.18	21,9
01.10.18	36,5
25.10.18	36,1
06.11.18	62,7
18.02.19	42,7

Abb. 11a: M2-PK Plasmatiter-Verlauf in Zahlen

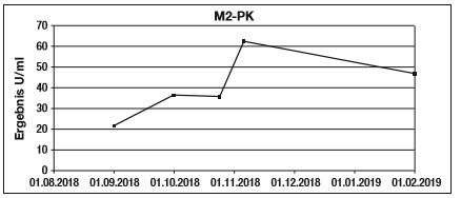
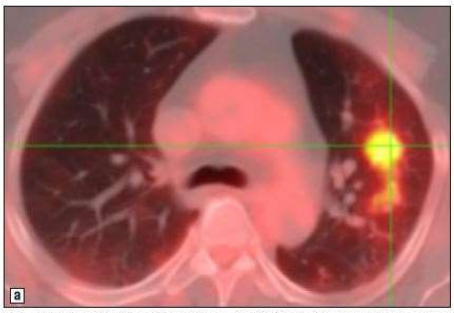


Abb. 11b: M2-PK Plasmatiter-Verlauf als Diagramm



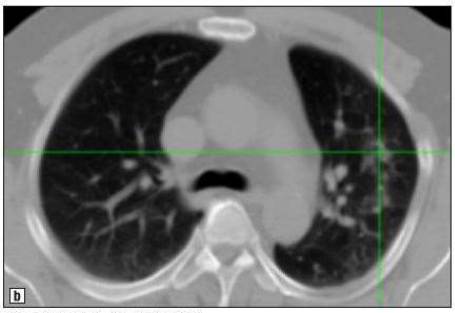


Abb. 12a und 12b: Onco-PET-CT vom 16.10.2018, Metastasenverdacht im FDG-Onco-PET-CT (li. OL, Karinahöhe)

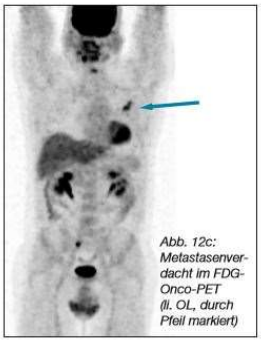


Abb. 12c: Metastasenverdacht im FDG-Onco-PET (li. OL, durch Pfeil markiert)

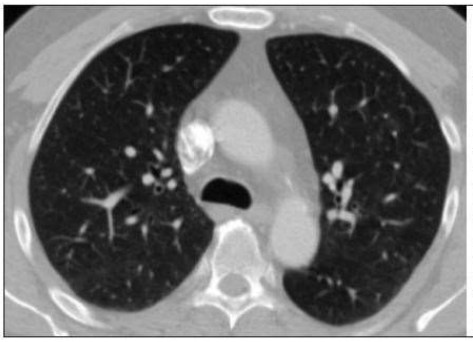


Abb. 12d: Kontrastmittel-CT des Thorax vom 06.11.2018 ohne jegliche persistierenden Infiltrationen oder gar Rundherde im vormals aspirationspneumonitisch alterierten li. Lungenoberlappen oder anderweitig pulmonal; identischer Befund am 05.03.2019 ohne Metastasen- oder Lokalrezidiv-Verdacht im KM-CT von Thorax und Abdomen nach 12 subkutanen Gepon®- bzw. Ezrin-Injektionen

Fall 6 – Beispiel einer zunehmenden Serum-Ca 19-9 Titererhöhung bei regredientem Tumorgeschehen unter bzw. nach Kombinationstherapie einer singulären Lebermetastase eines Pankreaskarzinoms.

Daten: W.B., geb. 08/46 mit Pankreaskopf-Karzinom (cT2, cN2, pM1<Leber>)

Z.n. explorativer Laparotomie 11/18 ohne chirurgische Kausaltherapie, nur unter Probeexzisionen aus einer singulären Lebermetastase (Segment III) bei lokal begrenztem Pankreaskopf-Karzinom.

Wegen fehlender weiterer Malignomausbreitung im ersten PET-CT (01/19) erfolgte die Planung eines auswärtigen nochmaligen chirurgischen Therapieversuchs für März /April 2019, falls die Patientin bis dato ohne Tumorprogress bleiben sollte. Tumormarker Ca 19-9 und M2-PK sind zwar aktuell noch ansteigend, anscheinend ist dies aber (post-)therapeutisch bedingt, da im aktuellen FDG-PETCT das Fehlen der Lebermetastase und eine diskrete Verkleinerung / Verminderung und Glukoseutilisation / Strahlungsintensität im Primärtumor auffällt. Die fakultative kurative OP ist jetzt für Ende April 2019 geplant, falls auch dann das aktuelle Leber-MRT keine weiteren Metastasen erkennen lässt. Aktuelle Therapie bis 02/19: hyperfraktionierte Ganzleber-Photonentherapie plus Metastasenboost in Segment III sowie gleichartige Photonentherapie des
Pan kreaskopftumors, in simultaner Kombination mit Insulin-potenzierter Lowdose-Chemotherapie gemäß Chemosensitivitätsergebnis (Institut Metavectum, Hamburg).

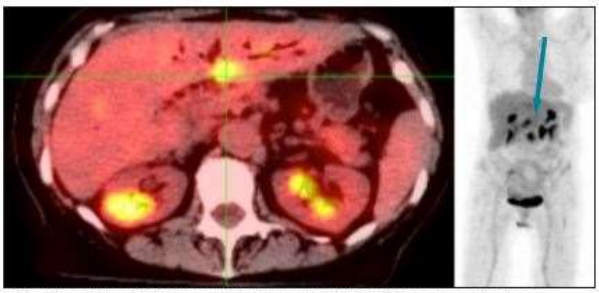


Abb. 13a, 13b: FDG-Onco-PET-CT vom 30.01.2019 Lebermetastase in Segment III (durch Fadenkreuz in 13a und blauen Pfeil in 13b markiert)

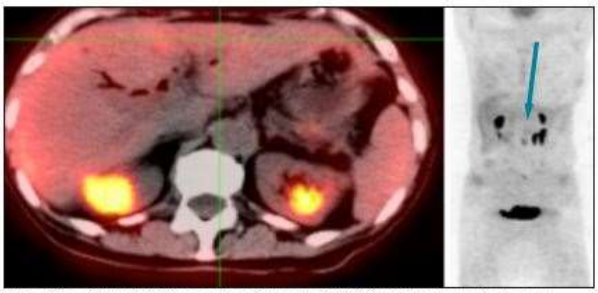


Abb. 13c, 13d: FDG-Onco-PET-CT vom 18.03.2019 Lebermetastase in Segment III nicht mehr nachweisbar (s. blauen Pfeil)

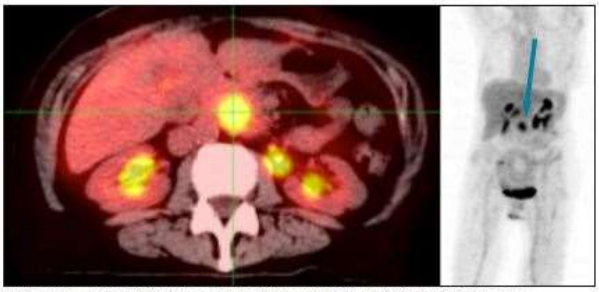


Abb. 14a, 14b: FDG-Onco-PET-CT vom 30.01.2019, Primärtumor im Pankreaskopf durch Fadenkreuz in 14a und blauen Pfeil in 14b markiert

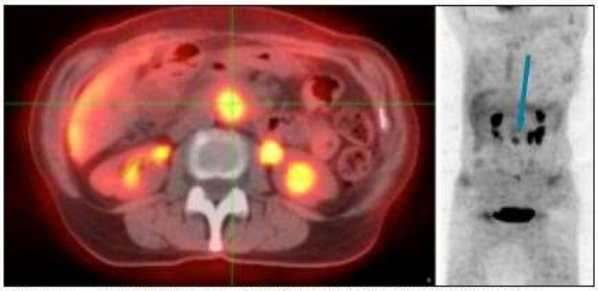


Abb. 14c, 14d: FDG-Onco-PET-CT vom 18.03.2019, Primärtumor im Pankreaskopf durch Fadenkreuz in 14c und blauen Pfeil in 14d markiert

Datum	Ergebnis
05.12.18	91,2
11.02.19	28,1
25.02.19	27,4
28.02.19	37
14.03.19	96,7

Abb. 15a: M2-PK Plasmatiter-Verlauf in Zahlen (U/ml)

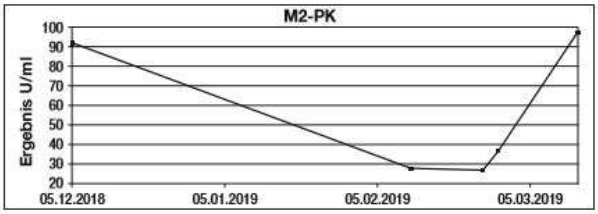


Abb. 15b: M2-PK Plasmatiter-Verlauf als Diagramm

Datum	Ergebnis	Datum	Ergebnis
05.12.18	527	28.01.19	470
17.12.18	355	04.02.19	597
02.01.19	318	11.02.19	535
10.01.19	429	25.02.19	537
14.01.19	328	28.02.19	646
21.01.19	448	14.03.19	971

Abb. 15c: Ca 19-9 Serumtiter-Verlauf in Zahlen (U/ml)

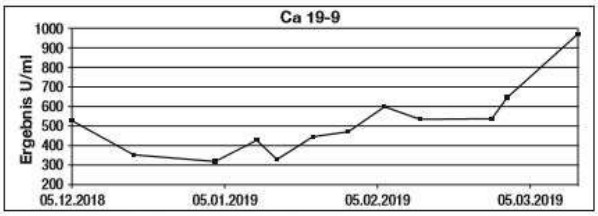


Abb. 15d: Ca 19-9 Serumtiter-Verlauf als Diagramm

Schlussbemerkungen

Die Konsequenzen, die sich für eine weiterführende Diagnostik, Therapie(änderung) und Prognose aus dem Verlauf von Tumormarkern ergeben, insbesondere wenn Titererhöhungen auch inflammatorisch (mit)bedingt sein könnten, müssen immer im Kontext a) mit der jeweiligen klinischen Symptomatik des Patienten wie beispielsweise einem möglichen Tumorzerfallsfieber unter

(Strahlen-)Therapie, b) mit CRP-Erhöhungen ohne direkten Anhalt für einen Infekt (Tumorentzündung!) und c) mit anderen Labor- und Blutbildparametern (Lymphozyten-Subtypisierung mit erhöhten T-reg. Lymphozyten) diagnostisch verwertet werden. Außerdem müssen a, b und c zusätzlich noch kumulativ in Synopse mit Behandlungsform, Primärtumorerkrankung und Krankheitsstadium sowie bildgebenden Verfahren – insbesondere PET-CT – betrachtet werden, um letztlich ausreichend valide Aussagen zu Tumorprogress und -regress oder stabilem Verlauf zu gewährleisten.

Dies ist die Voraussetzung für kurzfristige, Prognose-verbessernde Entscheidungen in Bezug auf Fortführung, Abänderung, Schwächung oder Verstärkung von Krebsbehandlungen, da man mit bloßen wiederholten Griffen nach medikamentösen Zweit-, Dritt- oder gar Viertlinien-Therapien seinen Patienten kaum gerecht werden kann. Mündet eine unzureichende Berücksichtigung einer eindeutig erkennbaren lokalen Begrenzung von Tumorrezidiven oder einer lokalen / lokoregionären Oligometastasierung in den sofortigen Beginn systemischer medikamentöser Behandlungen, belasten diese eventuell nur unnötig das zelluläre Immunsystem – und damit sogar die Prognose.

Tumormarker hingegen bieten gerade in solchen Fällen die hervorragende Möglichkeit, teure, ökonomisch obsolete, da frustran gewordene Medikationen früher als üblich abzusetzen, alternative Behandlungen möglichst lang anhaltend und im besten Sinne kontrolliert zu nutzen, dabei das Immunsystem der anvertrauten Krebspatienten zu schonen und ihnen insofern eine längere Zeitspanne zu ermöglichen, nicht am Leben vorbei zu überleben, sondern mitten im Leben zu verbleiben und es sogar genießen zu können.

Das soll jedoch keinesfalls bedeuten, dass in aussichtsreichen Fällen bei entspre chenden genetischen bzw. chromosomalen Tumorzellaberrationen (etwa aus Ko sten gründen oder wegen möglicher, auch tödlicher, Nebenwirkungen) me dika men töse onkologische Hemmstoff- oder Antikörperbe hand lun gen tunlichst ver mie den werden sollten. Sie dürften jedoch noch hint an gestellt werden, bis sich weniger komplizierte und nebenwirkungsärmere Behandlungsmethoden in ihrer Wirkung erschöpft haben sollten, zuallererst erkennbar an einer Erhöhung von Tumormarkertitern. Danach müssen selbstverständlich auch diese sog. „neuen Me tho den“ (= ATMP´s) mit all ihren positiven aber auch negativen Eigen schaften umgehend eingesetzt werden. Gemeinsam mit den vorangegangenen Behandlungen können sie anschließend das Überleben dieser Patienten eventuell noch weiter verlängern.

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New Look at an Old Principle: An Alternative Formulation of The Theorem of Minimum Entropy Production

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Abstract

We formulate a direct generalization of the Prigogine's principle of minimum entropy production, according to a new isoperimetric variation principle by classical non-equilibrium thermodynamics. We focus our attention on the possible mathematical forms of constitutive equations. Our results show that the Onsager's reciprocity relations are consequences of the suggested variation principle.

Furthermore, we show by the example of the thermo-diffusion such reciprocity relations for diffusion tensor, which are missing in Onsager's theory. Our theorem applied to the non-linear constitutive equations indicates the existence of dissipation potential. We study the forms of general reciprocity with the dissipation potential. This consideration results in a weaker condition than Li-Gyarmati-Rysselberhe reciprocity has. Furthermore, in the case of electric conductivity in the magnetic field, our theorem shows the correct dependence of the Onsager's kinetic coefficient by the axial vector of magnetic induction. We show in general that the evolution criterion of the global entropy production is a Lyapunov-function, and so the final stationer state is independent of the initial, time-independent boundary conditions.

Keywords: General Reciprocal Relations, Minimum-Entropy-Production, Bertalanffy's Equifinality

Introduction

The first formulation of the minimum entropy production for the non-continuous system was firstly formulated by Prigogine [1], [2]. This theorem was generalized by introducing the order of stationarity by de Groot [3]. The present theorem valid also for continuous systems and dealing with the dynamics and stability of the stationer systems was formulated by Glansdorff and Prigogine [4], [5]. Their work shows that the entropy production in the frame of linear Onsager's thermodynamic theory both the dynamics and the stability of the system correctly described, ranging the entropy production in the thermodynamics of linear stationer systems like the entropy in thermostatics. However, in the case of non-linear constitutive equations, this significant role of the entropy production vanishes and only the partial derivatives of entropy production by thermodynamical forces have such attributions like the entropy production itself in the linear Onsager's theory. Gyarmati had proved [6] that a realistic generalization of Onsager's principle of last dissipation of energy is equivalent to the above Glansdorff-Prigogine theorem. These considerations feature again the dissipation potentials introduced by Rayleigh and Onsager. The theories mentioned above emphasize a strong correlation between the existence of minimum entropy production and the possible form of constitutive equations of dissipative forces and currents.

Onsager proved the symmetry-relations and the potential dissipation behavior of entropy production by methods of fluctuation-theory. Hence the properties of constitutive equations connected to the extremal behavior of entropy production are not consistent with the field theory formulation of the non-equilibrium thermodynamics. In non-linear cases, unfortunately, such a generalized method does not exist to prove the potential behavior of the entropy production, (like for example to prove the higher-order Onsager's relations). However, by the strong correlation of the stationary behavior of the entropy production and the mathematical form of the constitutive equations, an interesting question arises: when we accept the extremal behavior of the entropy production what the consequences on the form of constitutive equations of non-linear thermodynamics are?

To study this, we investigate the constitutive equations with condition fix the extreme (more general stationer) behavior of the entropy production.

Materials and Methods

Formulation of the extremum principle

Let us study a stationer non-equilibrium thermodynamical system, containing a transport of n various in extensive, having ${}^{i}a$ and ${}^{i}\mathbf{j}$ densities and current-densities. We assume that the system is in cellular equilibrium. In this case, the Gibbs relation is valid, and the entropy density of the system (s) is a state-function of n different ${}^{i}a$ quantities. We define the conjugated intensives to ${}^{i}a$ extensive as:

$$ {}^{i}\Gamma = \frac{\partial s}{\partial\, {}^{i}a} \tag{1} $$

According to the second law of the non-equilibrium processes, the entropy production density of the system is:

$$ \sigma = \sum_{i=1}^{n} {}^{i}\mathbf{j} \cdot \nabla^{i}\Gamma \geq 0 \tag{2} $$

while ${}^{i}\Gamma^{i}\mathbf{j}$ entropy current transported together with the i-th extensive.

The complete entropy production (P) and the complete detailed entropy-flux (Φs) are:

$$ \begin{aligned} P &= \int_V \sigma\, dV = \int_V \sum_{i=1}^{n} {}^{i}\mathbf{j} \cdot \nabla^{i}\Gamma dV, \\ \Phi_s &= \oint_\Omega \sum_{i=1}^{n} {}^{i}\Gamma\ {}^{i}\mathbf{j} \cdot \mathbf{dA} = \int_V \sum_{i=1}^{n} \nabla \cdot \left({}^{i}\Gamma\ {}^{i}\mathbf{j}\right) dV \end{aligned} \tag{3} $$

where we used the Gauss-theorem in the second equation, and V and Ω are the volume and surface of the system, respectively. Simplifying the notations, we use the Einstein's sum-convention like:

$$ \begin{aligned} P &= \int_V \sum_{i=1}^{n} {}^{i}\mathbf{j} \cdot \nabla^{i}\Gamma dV := \int_V {}^{i}\mathbf{j} \cdot \nabla^{i}\Gamma dV \\ \Phi_s &= \oint_\Omega \sum_{i=1}^{n} {}^{i}\Gamma\ {}^{i}\mathbf{j} \cdot \mathbf{dA} := \oint_\Omega {}^{i}\Gamma\ {}^{i}\mathbf{j} \cdot \mathbf{dA} = \int_V \nabla \cdot \left({}^{i}\Gamma\ {}^{i}\mathbf{j}\right) dV \end{aligned} \tag{4} $$

The extremum theory of entropy production is formulated like a conditional extremum principle:

$$ P = \min, \qquad when \qquad \Phi_s = const \tag{5} $$

This could be more precisely written in the isoperimetric variation-principle:

$$S=\int_V LdV = stac, \quad L:=(\lambda+1)\ {}^i\mathbf{j}\cdot\nabla^i\Gamma+\lambda^i\Gamma\nabla\cdot{}^i\mathbf{j} \tag{6}$$

where λ is a constant scalar multiplicator. This isoperimetric variation task could be reformulated by dual form when we investigate the conditional stationarity of Φs concerning constant P. In this case, the variation-principle and the Lagrangian are:

$$S=\int_V LdV = stac, \quad L:=(\lambda+1)^i\Gamma\nabla\cdot{}^i\mathbf{j}+\lambda\ {}^i\mathbf{j}\cdot\nabla^i\Gamma \tag{7}$$

The case of linear constitutive laws

The material equations are:

$$\nabla^i\Gamma=\mathbf{R}_{ik}{}^k\mathbf{j} \tag{8}$$

where Rik is the second-order tensor of the Onsager's kinetic coefficients, characteristic for the given material. In consequence of (7) the actual form of the Lagrangian is:

$$L=(\lambda+1)\ {}^i\Gamma\nabla\cdot{}^i\mathbf{j}+\lambda\mathbf{R}_{ik}{}^k\mathbf{j}\cdot{}^i\mathbf{j}+ \tag{9}$$

The Euler-Lagrange- equation belonging to the variation of the current densities as sufficient condition for an extremum is:

$$\lambda\left(\mathbf{R}_{ik}+\mathbf{R}_{ki}^T\right)^k\mathbf{j}=(\lambda+1)\mathbf{R}_{ik}{}^k\mathbf{j} \quad \rightarrow \quad \lambda\mathbf{R}_{ki}^{T\ k}\mathbf{j}=\mathbf{R}_{ik}{}^k\mathbf{j} \tag{10}$$

where the upper index T refers to the transpose of the tensor.

The entropy-production from this considering its constant demand, we get:

$$\lambda\mathbf{R}_{ik}^{T\ i}\mathbf{j}\cdot{}^k\mathbf{j}=\mathbf{R}_{ik}{}^k\mathbf{j}\cdot{}^i\mathbf{j} \tag{11}$$

It could be valid in all the arbitrary cases of current densities only, when λ=1, so the following Onsager's symmetry-relations are valid:

$$\mathbf{R}_{ki}^T=\mathbf{R}_{ik} \tag{12}$$

The entropy-production will be minimal in this case, and this result remains valid in the case of quasi-linear constitutive cases as well. The symmetry-relations in (12) are more general than the original Onsager's theory. This will be shown in the case of the thermo-diffusion.

Results and Discussion

$$P=\int_V\left[{}^q\mathbf{j}\cdot\nabla\left(\frac{1}{T}\right)-{}^\alpha\mathbf{j}\cdot\nabla\left(\frac{{}^\alpha\mu}{T}\right)\right]dV= \tag{13}$$

$$=\int_V\left[{}^q j^i\frac{\partial}{\partial x^i}\left(\frac{1}{T}\right)-{}^\alpha j^i\frac{\partial}{\partial x^i}\left(\frac{{}^\alpha\mu}{T}\right)\right]dV$$

$$\Phi_s = \int_V \left[\frac{1}{T} \nabla \cdot {}^q\mathbf{j} + {}^q\mathbf{j} \cdot \nabla \left(\frac{1}{T} \right) - \frac{{}^\alpha\mu}{T} \nabla \cdot {}^\alpha\mathbf{j} - {}^\alpha\mathbf{j} \cdot \nabla \left(\frac{{}^\alpha\mu}{T} \right) \right] dV = \tag{14}$$

$$= \int_V \left[\frac{1}{T} \frac{\partial {}^q j^i}{\partial x^i} + {}^q j^i \frac{\partial}{\partial x^i} \left(\frac{1}{T} \right) - \frac{{}^\alpha\mu}{T} \frac{\partial {}^\alpha j^i}{\partial x^i} - {}^\alpha j^i \frac{\partial}{\partial x^i} \left(\frac{{}^\alpha\mu}{T} \right) \right] dV$$

Thermodiffusion in the triclinic system

In the case of thermodiffusion the global entropy-production and the detailed global entropy flux are [6]:

Let us consider the following linear constitutive equations:

$$\frac{\partial}{\partial x^i} \left(\frac{1}{T} \right) = \mathrm{K}_{ik} \, {}^q j^k - {}^\alpha \mathrm{K}_{ik} \, {}^\alpha j^k \tag{15}$$

$$\frac{\partial}{\partial x^i} \left(\frac{{}^\alpha\mu}{T} \right) = - {}^{\alpha\beta} D_{ik} \, {}^\beta j^k - D_{ik} \, {}^q j^k$$

With these equations the Lagrangian of (7) is:

$$L = \frac{\lambda + 1}{T} \frac{\partial {}^q j^i}{\partial x^i} + (\lambda + 1) \frac{{}^\alpha\mu}{T} \frac{\partial {}^\alpha j^i}{\partial x^i} + \lambda (\mathrm{K}_{ik} \, {}^q j^i \, {}^q j^k - {}^\alpha \mathrm{K}_{ik} \, {}^q j^i \, {}^\alpha j^k \tag{16}$$

$$- D_{ik} \, {}^q j^i \, {}^\alpha j^k - {}^{\alpha\beta} D_{ik} \, {}^\alpha j^i \, {}^\beta j^k)$$

Determination of the kinetic coefficients of (15) is possible from the Euler-Lagrange- equations belonging to the variation of i-th coordinate qji and αji of the heat and α-the chemical component current densities:

$${}^q j^i (\lambda \mathrm{K}_{ik} - \mathrm{K}_{ik}) + {}^\alpha j^i \left(\lambda \, {}^\alpha \mathrm{K}_{ki} - D_{ik} \right) = 0 \tag{17}$$

$${}^q j^i \left(\lambda \, {}^\alpha \mathrm{K}_{ki} - D_{ik} \right) + {}^\alpha j^i \left(\lambda \, {}^{\alpha\beta} D_{ik} - {}^{\beta\alpha} D_{ki} \right) = 0$$

From these (due to the arbitrary current densities) we receive:

$${}^q j^i (\lambda \mathrm{K}_{ik} - \mathrm{K}_{ik}) = 0 \tag{18}$$

$${}^\alpha j^i \left(\lambda \, {}^\alpha \mathrm{K}_{ki} - D_{ik} \right) = 0$$

$${}^\alpha j^i \left(\lambda \, {}^{\alpha\beta} D_{ik} - {}^{\beta\alpha} D_{ki} \right) = 0$$

Using the (14) the λ=1, and hence we get the symmetry relations:

$$\mathrm{K}_{ik} = \mathrm{K}_{ik}, \quad {}^\alpha \mathrm{K}_{ki} = D_{ik}, \quad {}^{\alpha\beta} D_{ik} = {}^{\beta\alpha} D_{ki} \tag{19}$$

Last relations obtained elements of diffusion tensor αβDik are more general than found in the available literature [7].

General evaluation of the extremum principle: Based on the above description we show below an essential consequence of the extremum principle: it is the existence of the dissipation potential for the case of non-linear constructive equations. Very general symmetry relations (like was established by Li-Gyarmati-Rysselberghe [8], [9], [10]) are the consequence of the dissipation potential. Suppose n different constitutive equations describe the system, instead of the linear constitutive equations (8). In this case, the Euler-Lagrange equations as conditions of extremum are:

$$\nabla^i \Gamma = {}^i\mathbf{f}\left({}^j\Gamma, {}^j\mathbf{j}\right) \tag{20}$$

$${}^j\mathbf{f} = \lambda \frac{\partial^i \mathbf{f}}{\partial^j \mathbf{j}}\, {}^i\mathbf{j} \tag{21}$$

Using (21), we get the following derivative tensors:

$$\frac{\partial^j \mathbf{f}}{\partial^i \mathbf{j}} = \lambda \left(\frac{\partial^i \mathbf{f}}{\partial^j \mathbf{j}} + \frac{\partial^2\, {}^i\mathbf{f}}{\partial^i \mathbf{j} \partial^j \mathbf{j}}\, {}^i\mathbf{j} \right), \quad \frac{{}^i\mathbf{f}}{\partial^j \mathbf{j}} = \lambda \left(\frac{\partial^j \mathbf{f}}{\partial^i \mathbf{j}} + \frac{\partial^2\, {}^j\mathbf{f}}{\partial^j \mathbf{j} \partial^i \mathbf{j}}\, {}^j\mathbf{j} \right) \tag{22}$$

Assuming the continuity of second-order derivatives, using Young's theorem, we obtain generalized reciprocity relations:

$$\frac{\partial^j \mathbf{f}}{\partial^i \mathbf{j}} = \frac{{}^i\mathbf{f}}{\partial^j \mathbf{j}} \tag{23}$$

These relations are necessary and sufficient for the existence of a $\Phi({}^j\Gamma, {}^j\mathbf{j})$ dissipation potential with the conditions:

$$\nabla^i \Gamma = {}^i\mathbf{f} = \frac{\partial \Phi}{\partial^i \mathbf{j}}, \quad {}^i\mathbf{j} \cdot \frac{\partial \Phi}{\partial^i \mathbf{j}} \geq 0, \quad \left. \frac{\partial \Phi}{\partial^i \mathbf{j}} \right|_{{}^j\mathbf{j}=0} = 0 \tag{24}$$

The dissipation potential is tightly connected to the entropy production density.

To show this calculation, the partial derivatives of σ by ${}^i\mathbf{j}$ and using (21), we get from (2):

$$\frac{\partial \sigma}{\partial^i \mathbf{j}} = {}^i\mathbf{f} + \frac{\partial^i \mathbf{f}}{\partial^i \mathbf{j}}\, {}^i\mathbf{j} = \frac{\lambda+1}{\lambda}\, {}^i\mathbf{f} = \frac{\lambda+1}{\lambda} \frac{\partial \Phi}{\partial^i \mathbf{j}} \tag{25}$$

In consequence:

$$\sigma = \frac{\lambda+1}{\lambda} \Phi + \Phi_0\left({}^j\Gamma\right) \tag{26}$$

moreover, from (24) follows:

$$ {}^{i}\mathbf{j}\cdot\frac{\partial\sigma}{\partial\,{}^{i}\mathbf{j}}=\frac{\lambda+1}{\lambda}{}^{i}\mathbf{j}\cdot{}^{i}\mathbf{f}=\frac{\lambda+1}{\lambda}\sigma \quad (27)$$

Disregarding the scalar function $\Phi_0({}^{j}\Gamma)$ which depends only on the intensives, in consequence of (26) and (27) the dissipation potential satisfies the following significant relation:

$$ {}^{i}\mathbf{j}\cdot\frac{\partial\Phi}{\partial^{i}\mathbf{j}}=\frac{\lambda+1}{\lambda}\Phi=\Theta\Phi,\quad \Theta=\frac{\lambda+1}{\lambda} \quad (28)$$

Hence the dissipation potential Φ is Θ-the order homogenous Euler-function of the current transport densities. The entropy production density is zero at zero current densities, so Θ >0. However, due to the non-negativity of entropy production, Θ≥2, and an integer. In the case of Θ=2 the constitutive equations are linear, the reciprocity relations are Onsager-type and the Lagrange multiplicator λ=1.

The Li-Gyarmati-Rysselberghe's non-linear constitutive equations are derived from the Taylor series of the general equation (20):

$$ \nabla^{i}\Gamma={}^{i}\mathbf{f}\left({}^{j}\Gamma,{}^{j}\mathbf{j}\right)\cong{}^{i}\mathbf{R}_{j}{}^{j}\mathbf{j}+{}^{i}\mathbf{R}_{jk}{}^{j}\mathbf{j}^{k}\mathbf{j} \quad (29)$$

where ${}^{i}\mathbf{R}_{j}$ és ${}^{i}\mathbf{R}_{jk}$ are the second- and third-order tensors of the kinetic coefficients.

As we have seen above, in consequence of the various principles the dissipation potential is a homogeneous Euler function of the current transport densities. On the other hand, the first-order partial derivatives of the Euler functions (in our case the constitutive equations) are also Euler functions having an order less than the original was. Because the constitutive equations (29) are not homogeneous Euler functions, they cannot be derived from the dissipation potential. Consequently the linear equation alternatively, the second-order equation

$$ \nabla^{i}\Gamma={}^{i}\mathbf{f}\left({}^{j}\Gamma,{}^{j}\mathbf{j}\right)\cong{}^{i}\mathbf{R}_{j}{}^{j}\mathbf{j} \quad (30)$$

$$ \nabla^{i}\Gamma={}^{i}\mathbf{f}\left({}^{j}\Gamma,{}^{j}\mathbf{j}\right)\cong{}^{i}\mathbf{R}_{jk}{}^{j}\mathbf{j}^{k}\mathbf{j} \quad (31)$$

could be derived from the potentials of second- and third-order. These could be constructed, for example, by the method of Vainberg [11] as follows:

$$ {}^{(2)}\Phi\left({}^{j}\Gamma,{}^{j}\mathbf{j}\right)=\int_{0}^{1}{}^{j}\mathbf{j}\cdot{}^{i}\mathbf{R}_{j}\left(\tau\,{}^{j}\mathbf{j}\right)d\tau=\frac{1}{2}{}^{j}\mathbf{j}\cdot{}^{i}\mathbf{R}_{j}{}^{j}\mathbf{j} \quad (32)$$

$$ {}^{(3)}\Phi\left({}^{j}\Gamma,{}^{j}\mathbf{j}\right)=\int_{0}^{1}{}^{j}\mathbf{j}\cdot{}^{i}\mathbf{R}_{jk}\left(\tau\,{}^{j}\mathbf{j}\right)\left(\tau^{k}\mathbf{j}\right)d\tau=\frac{1}{3}{}^{j}\mathbf{j}\cdot{}^{i}\mathbf{R}_{jk}{}^{j}\mathbf{j}^{k}\mathbf{j}$$

From the above potentials, we get in the case of the linear equation the while in non-linear case the reciprocal relations.

$$ {}^{i}\mathbf{R}_{j}=\left({}^{j}\mathbf{R}_{i}\right)^{T} \quad (33)$$

$$ {}^{i}\mathbf{R}_{jk} = \left({}^{j}\mathbf{R}_{ik}\right)^{TT} \tag{34} $$

These last reciprocal relations are weaker than the Li-Gyarmati-Rysselberghe's because that allows changing the cycle of the indexes of the third-order kinetic tensor, while (34) does not change the cycle of the indexes, only shifts ahead twice the last index, ie.

$$ {}^{i}R_{uvw} = {}^{i}R_{vwu} \tag{35} $$

Also, these relations are a generalization of Li-Gyarmati-Rysselberghe-type reciprocal relation. The original reciprocity was introduced by Onsager for the case of α-type variables having even-functions of the velocities of molecular particles [12], [13]. This was generalized by Casimir for β-type variables, having odd-functions of the given velocities, [14]. The generalized reciprocity relations containing both the conditions are called Casimir-Onsager-reciprocity relation, (CORR). Due to the unreasoning meaning of the velocity in quantum-mechanical conditions, there are certain doubts about the correctness of CORR.

On the other hand in case of the magnetic field and rotating movements for the reversibility of the orbits of particles the mirroring of the axial vectors (like B and ω) is necessary. Accepting, however, the role of the molecular velocities in CORR, the mirroring has to be seen in the constitutive equations too. This is investigated below connected to the electric conductivity in triclinic system.

Electric conductivity in the triclinic system in the presence of external magnetic field

For simplicity, we suppose the investigated process is isotherm. In this case, the entropy density and the specific entropy current density could be written as:

$$ \sigma = \frac{1}{T}\mathbf{j}\cdot\mathbf{E} = -\frac{1}{T}\mathbf{j}\cdot\nabla\varphi, \quad \mathbf{j}_s = -\frac{1}{T}\mathbf{j}\varphi \tag{36} $$

where the intensity parameter φ is the electric potential. The linear constitutive equation is:

$$ \nabla\varphi = -\mathbf{R}\mathbf{j} - \kappa\,\mathbf{j}\times\mathbf{B} := \mathbf{R}(\mathbf{B})\mathbf{j}, \quad \frac{\partial\varphi}{\partial x_i} = -R_{ij}j_j - \kappa\varepsilon_{ijk}j_jB_k \tag{37} $$

where R is the specific resistivity tensor of the given crystal, κ is constant material characteristics, and εijk is a permutation symbol, equal 1 when the series of I,j,k is even or -1 when odd permutation of numbers 1,2,3. The corresponding Lagrangian is:

$$ L = -(\lambda+1)\varphi\frac{\partial j_i}{\partial x_i} + \lambda R_{ij}j_ij_j + \lambda\kappa\varepsilon_{ijk}j_ij_jB_k \tag{38} $$

With a variation of the j-th coordinate j_j of electric current density, we get the following Euler-Lagrange-equations:

$$ \begin{aligned} &\lambda\left(R_{ij} + R_{ji}\right)j_i + \lambda\kappa\left(\varepsilon_{ijk}j_iB_k + \varepsilon_{jik}j_iB_k\right) = \\ &= (\lambda+1)\left(R_{ij}j_i + \varepsilon_{ijk}j_iB_k\right) \end{aligned} \tag{39} $$

which by algebraic rearrangement leads to the equations:

$$\lambda R_{ji} j_i + \lambda \kappa \varepsilon_{jik} j_i B_k = R_{ij} j_i + \varepsilon_{ijk} j_i B_k \quad (40)$$

Regarding the λ=1 in case of linear constitutive equations as is, we receive the relations:

$$R_{ji} j_i + \kappa \varepsilon_{jik} j_i B_k = R_{ij} j_i + \kappa \varepsilon_{ijk} j_i B_k \quad (41)$$

which is valid for every j_j and Bk. However it could be satisfied only when the elements of the resistivity tensor

$$R_{ij}(B) := R_{ij} + \kappa \varepsilon_{ijk} B_k, \quad (i, j, k = 1,2,3) \quad (42)$$

satisfy the well-known reciprocity relations.

$$R_{ij}(B) := R_{ji}(-B) \quad (43)$$

A nonlinear generalization of the Prigogine-Glansdorff's evolution criterion

Introducing the dissipation potentials depending on the thermodynamic forces by Legendre transformation:

$$\Psi\left(\nabla^j \Gamma\right) = {}^i\mathbf{j} \cdot \nabla^i \Gamma - \Phi\left({}^j\mathbf{j}\right) = \sigma - \Phi\left({}^j\mathbf{j}\right) \quad (44)$$

In this case, using (26) we obtain:

$$\Psi = \frac{1}{1+\lambda}\sigma \quad (45)$$

Hence

$$\frac{d}{dt}\int_V \Psi dV = \frac{1}{1+\lambda}\frac{d}{dt}\int_V \sigma dV = \frac{1}{1+\lambda}\frac{dP}{dt} \quad (46)$$

It was shown by Prigogine and Glansdorff that the Ψ thermodynamic potential depending on the thermodynamic forces at time-independent boundary conditions satisfies the following general condition of evolution:

$$\frac{d}{dt}\int_V \Psi dV \le 0 \quad (47)$$

In consequence of this and (44) the global entropy production (in the same way as was in the case of linear constitutive equations) satisfies the following general criterion of evolution:

$$\frac{dP}{dt} = \frac{d}{dt}\int_V \sigma dV \le 0 \quad (48)$$

This means that the global entropy production of a system with time-independent boundary conditions always decreases, till it reaches its stationer value determined by the global entropy-flux as a restriction.

When the global entropy production in case the fluctuations of the thermodynamical forces and the current densities satisfy the condition:

$$\delta P \geq 0 \qquad (49)$$

Then the stationary value is minimum, and regarding the (48) evolution criterion of the global entropy production is a Lyapunov-function. It has two significant consequences. First is that the stationer state is stable, and second that the system starting in any neighboring states of the final stationer, one always reaches the same final state by its evolution. Shortly: these systems (in this general formulation also) show the Bertalanffy's equifinal behaviour [15].

Conclusions

We have demonstrated, that a suggested modification of the principle of minimum entropy production has essential applications in the theory of constitutive laws of non-equilibrium thermodynamics, including reciprocal relations. In the rigorous phenomenology, we may regard the reciprocal relations as experimentally proven axioms, or we have to derive them on the direct phenomenological way. We have to accept the opinion of Truesdell [16]: „if the reciprocal relations are true, we have to derive them by pure phenomenology also". We did this job, showing the Onsager's reciprocal relations and their dependence on magnetic induction field is a consequence of a phenomenological variations principle in the frame of linear constitutive equations. The existence of the dissipation potential is a consequence of the various principles, which was valid only in linear cases till now. In non-linear cases, these relations can be derived from a dissipation potential which is the homogeneous function of the current transport densities. The potential is at the same time assures the validity of the more general reciprocal relations than the Onsager's. We had shown furthermore, that compatible theory with dissipation potential does not exist in the case of Li-Gyarmati–Rysselberghe's constitutive equation; which anyway is frequently used in the non-equilibrium thermodynamics, because these are not homogeneous Euler's functions.As a consequence of this and the general reciprocal relations, we have limits for the kinetic tensors of the Taylor approximation. The second-order tensor in the linear approximation shows asymmetry relation which is identical with the well-known Onsager's reciprocal relation. This result suggests that the Onsager's reciprocal relations are general in linear cases. Consequently, this approximation is same accurate as the linear case itself.

In linear theory, the global entropy production decreased by evolution to stationer state (at constant boundary conditions) and became minimal when the system reaches its stationary case. Consequently, the derivative of the global entropy production concerning time is nonpositive. Two parts of the time-derivative of global entropy production (containing the time-derivatives of the thermodynamical forces and the time derivatives of thermodynamical currents) are equal and decreasing with the time-evolution of the system, realizing the minimal entropy production conditions. In non-linear case, the part that contains the time- derivatives of the thermodynamical forces decreases in the same way as in the linear one. However, we have no information about another part that contains the time-derivation of the thermodynamical currents. By Legendre transformation of the dissipation potentials depending on the current densities introduced another dissipation potential, which is a function of thermodynamic forces and we had proven their proportionality to the density of entropy-production. According to Prigogine-Glansdorff's evolution criterion and the properties of Legendre transformation, the time-derivative of this dissipation function is nonpositive.

Consequently, the global entropy production decreases in every case and has a similar role in this non-linear theory as the entropy has in the linear thermodynamics. In consequence of this, the Prigogine-Glansdorff's general evolution criteria are valid for the global entropy production like it is valid in the linear theory. When in stationer state the global entropy production of a system has a local minimum than it is described by a Lyapunov function. According to Bertalanffy, this system is equifinal, having equivalent final state starting in the vicinity of the stationer state. In case of convex dissipative functions when the local and global minima are equal, all the initial states are equifinal.

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Advertisement

Buddies For Life Magazine: Hyperthermia and breast cancer

We learn more about the new treatment, hyperthermia and its benefits when applied in conjunction with chemotherapy and radiation for the treatment of breast cancer.

In oncology, hyperthermia is the heating up of tumours to above 39°C. Hyperthermia is sometimes applied to tumours that are particularly difficult to treat, to sensitise the tumours to the prescribed treatments (radiotherapy or chemotherapy).

Hyperthermia is sometimes used to treat a local recurrence in the chest wall from breast cancer after prior treatment with radiotherapy to the region has failed.

Tumour changes

Several changes begin to happen in a tumour that has been heated, which results in an increase in the sensitivity of the tumour to either chemotherapy or radiotherapy.

The first change that begins to happen is an increase in the blood flow to the tumour. This is helpful when given in combination with chemotherapy as the increased blood flow increases the delivery and concentration of chemotherapy in the tumour.

Radiation works best in tissues that have adequate levels of oxygen in them. Very large tumours, or tumours that have recurred in a previously treated region often have low levels of oxygen.

The increased blood flow from the heating also increases the amount of oxygen in the tumour which helps the radiation to be more effective at killing the tumour. When combined with radiation, hyperthermia is usually given once or twice a week, after the radiotherapy appointment.

Other benefits of heating include an inhibition of the tumour cells' ability to repair from the damage done by the chemotherapy or radiotherapy and a stimulation of the immune response at the heated site.

Breast cancer

Tumours in the breast are considered to be superficial. This means that they are easily targeted with a variety of hyperthermia technologies and can be fairly easily heated, without heating the surrounding tissues.

The standard treatment for breast cancer is chemotherapy, surgery and radiotherapy. This combination usually works very well, especially if the cancer is detected early enough. The need for hyperthermia in the early stages of breast cancer is therefore very low.

Hyperthermia may still be beneficial in instances where breast tumours are very large and difficult to operate on and which don't respond well to chemotherapy. In these cases, there may be a benefit to adding hyperthermia to radiotherapy treatment.

The most well-known indication for hyperthermia in the management of breast cancer is for recurrent tumours. In cases where there is a recurrence in the skin or lymph nodes in the chest area which was previously treated with radiotherapy, the recurrent tumours may be resistant to radiotherapy.

It can be dangerous to give more radiation to an area that has already been treated with radiotherapy, as the healthy tissues are at risk of over exposure. There is a lot of research indicating that giving a lowered dose of radiotherapy, combined with hyperthermia, to the recurrent area, is an effective way to manage these difficult to treat cases.

What kinds of hyperthermia can be used for breast cancer?

Superficial heating techniques for breast tumours include using water-filtered infrared-light, or radiofrequency waves, to heat the area.

The biggest risk is the accidental burning of the skin during the heating process, although the safety of the newer technologies has reduced this risk to below 1%.

Infrared-heating needs to be applied immediately before radiotherapy and there can only be a gap of five minutes between the heating and the start of the radiotherapy.

In SA only radiofrequency heating is currently available. This involves the placement of an electrode over the affected area, for 30 to 60 minutes, after radiotherapy.

Are you eligible for hyperthermia?

Your oncologist needs to decide if you could benefit from it. If you're eligible, then he/she will prescribe the treatment and refer you to a hyperthermia unit.

The treatments are currently only available at the Wits Donald Gordon Medical Centre and unfortunately, the treatments are not yet covered by medical schemes.

MEET OUR EXPERT – Dr. Carrie Minnaar

Dr. Carrie Minnaar first studied hyperthermia in Germany in 2009 and completed her PhD on hyperthermia in oncology at Wits in 2019. Currently, Dr. Minnaar practices oncologic hyperthermia at the Wits Donald Gordon Medical Centre.

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