ONCOTHERMIA JOURNAL

A publication of Oncotherm® ISSN 2191-6438

Volume 32 - September 2022

Imprint

Editorial

Dear Reader, Dear Fellow Researchers, Dear Colleagues,

Oncotherm considers it very important to inform those who are interested in the latest results of hyperthermia and the trends on the emerging field of oncology. You presently reading the 32nd volume of this informative publication. The Oncothermia Journal continues to provide resources for clinical practices and research experts, offering new possibilities to treat patients where conventional oncotherapies have ceased to apply.

The articles of this volume partly cover presentations of clinicians using hyperthermia and indicating impressive results in the 39th Conference of International Clinical Hyperthermia Society (ICHS). Due to the COVID restrictions, the conference was held online. Renowned professionals from various countries contributed with their clinical results and views about the bright perspectives for the future of hyperthermia.
Professor Dr. Stephan Bodis (Zurich University, Switzerland) had integrated the worldwide achieved clinical results and expressed his conviction towards the use of hyperthermia as an excellent complementary treatment to radiotherapy. He presented the current status of the method in Switzerland, which could be exemplary for other countries too.
Prof. Dr. Elisabeth Arrojo (Valdecilla University, Spain) highlighted the preliminary results of the started Phase III glioblastoma trials with modulated electrohyperthermia (mEHT). The professional team of the dedicated Hyperthermia Department of Valdecilla University has high hopes for its success.
Dr. Carrie Minnaar (Johannesburg University, South Africa) presented the follow-up of the very successful mEHT Phase III clinical trial of advanced cervix cancer patients. It is remarkable that both the survival time and the quality of life improved significantly and synergically in the three-year follow-up period. The two exciting articles describe the achievement of her team.
Immunotherapy is one of the emerging areas of oncology. Prof. Dr. Stefaan van Gool (Immune-oncology Center Cologne, Germany) examined the immune activation with Newcastle viruses to temozolomide and mEHT complementary therapy, showing remarkable improvements in the treatment of patients suffering from glioblastoma multiform.
The hepato-pancreato-biliary system has not achieved sufficient success yet in conventional therapies. Dr. Marcell Attila Szasz (Semmelweiss University, Hungary) presented a preliminary result in treating this complicated disease with mEHT. The work continues, and the team expects to make a new protocol for this severe malignant localization.
Our goal is to provide relevant and up-to-date information for your clinical practices. I hope this volume can be beneficial to your daily treatment decisions with its useful observations.
Enjoy this 32nd volume of the Oncothermia Journal!

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

Liebe Leserinnen und Leser, liebe Forscherkollegen, liebe Kolleginnen und Kollegen,

Oncotherm hält es für sehr wichtig, diejenigen zu informieren, die an den neuesten Ergebnissen der Hyperthermie und den Trends auf dem aufstrebenden Gebiet der Onkologie interessiert sind. Sie lesen gerade den 32. Band dieser informativen Publikation. Das Oncothermia Journal stellt weiterhin Ressourcen für klinische Praxen und Forschungsexperten bereit und bietet neue Möglichkeiten zur Behandlung von Patienten, bei denen herkömmliche Onkotherapien nicht mehr greifen.
Die Artikel dieses Bandes umfassen zum Teil Präsentationen von Kliniken, die Hyperthermie anwenden und beeindruckende Ergebnisse auf der 39. Konferenz der International Clinical Hyperthermia Society (ICHS) vorlegen. Aufgrund der COVID-Beschränkungen wurde die Konferenz online abgehalten. Renommierte Fachleute aus verschiedenen Ländern trugen mit Ihren klinischen Ergebnissen und Ansichten über die vielversprechenden Zukunftsaussichten der Hyperthermie bei.
Professor Dr. Stephan Bodis (Universität Zürich, Schweiz) stellte die weltweit erzielten klinischen Ergebnisse vor und äußerte seine Überzeugung, dass die Hyperthermie eine hervorragende Ergänzung zur Strahlentherapie darstellt. Professor Dr. Stephan Bodis präsentierte den aktuellen Stand der Methode in der Schweiz, der auch für andere Länder beispielhaft sein könnte.
Prof. Dr. Elisabeth Arrojo (Universität Valdecilla, Spanien) stellte die vorläufigen Ergebnisse der begonnenen Phase-III-Glioblastom-Studien mit modulierter Elektrohyperthermie (mEHT) vor. Das professionelle Team der Abteilung für Hyperthermie an der Universität Valdecilla setzt große Hoffnungen in den Erfolg dieser Methode.
Dr. Carrie Minnaar (Universität Johannesburg, Südafrika) stellte die Ergebnisse der sehr erfolgreichen klinischen Phase-III-Studie mit mEHT bei Patienten mit fortgeschrittenem Gebärmutterhalskrebs vor. Es ist bemerkenswert, dass sich sowohl die Überlebenszeit als auch die Lebensqualität in der dreijährigen Nachbeobachtungszeit signifikant und synergetisch verbessert haben. Die beiden spannenden Artikel beschreiben die Leistung Ihres Teams.
Die Immuntherapie ist einer der aufstrebenden Bereiche der Onkologie. Prof. Dr. Stefaan van Gool (Immunonkologisches Zentrum Köln, Deutschland) untersuchte die Immunaktivierung mit Newcastle-Viren als Ergänzung zur Temozolomid- und mEHT-Therapie und zeigte bemerkenswerte Verbesserungen bei der Behandlung von Patienten mit Glioblastoma multiform.
Für das Leber-Pankreas-Galle-System konnten mit konventionellen Therapien noch keine ausreichenden Erfolge erzielt werden. Dr. Marcell Attila Szasz (Semmelweiss Universität, Ungarn) präsentierte ein erstes Ergebnis bei der Behandlung dieser komplizierten Krankheit mit mEHT. Die Arbeit geht weiter, und das Team erwartet, ein neues Protokoll für diese schwere bösartige Lokalisation zu erstellen.
Unser Ziel ist es, relevante und aktuelle Informationen für Ihre klinische Praxis bereitzustellen. Ich hoffe, dass dieser Band mit seinen nützlichen Beobachtungen für Ihre täglichen Behandlungsentscheidungen von Nutzen sein kann.
Viel Spaß mit dieser 32. Ausgabe des Oncothermia Journal!

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

   Manuskripte können online eingereicht werden: info@oncotherm.org

3. **Preparation of Manuscripts**

   Manuscripts must be written in English, but other languages can be accepted for special reasons, if an English abstract is provided.
   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
- Tables and Figures: Tables and figures should be referred to in the text (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without a reference to the text. Figure files will ideally be submitted as a jpg-file (300dpi for photos).
- 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.

Manuskripte vorbereiten

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.

Manuskripte können jede Länge haben, müssen aber die folgenden Punkte erfüllen:

- Titelseite: Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte, mindestens ein Autor muss genannt werden, E-Mail-Adresse und Kontaktdetails des Autors
- 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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When the proofs are ready, the corresponding authors will receive an e-mail notification. Hard copies of proofs will not be mailed. To avoid delays in the publication, corrections to proofs must be returned within 48 hours, by electronic transmittal or fax.

Elektronische Korrekturfahne

Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per E-Mail informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhindern, müssen die korrigierten Texte innerhalb von 48 Stunden per E-Mail oder Fax zurückgesandt werden.

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Werbung

Das Oncothermia Journal akzeptiert Werbeanzeigen in allen Sprachen, bevorzugt, aber die zumindest teilweise Gestaltung in englischer Sprache. Die Werbung muss eine Beziehung zu den Themen des Oncothermia Journals haben und der Wahrheit entsprechende Inhalte aufweisen.

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Haftung

Die Autoren aller im Oncothermia Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das Oncothermia Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Die Redaktion hat das Recht Artikel abzulehnen.

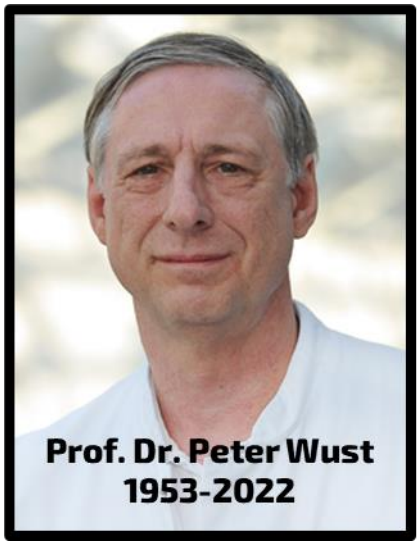
9. **Reviewing**

The Oncothermia Journal has a special peer-reviewing process, represented by the editorial board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of the reviewer will not be released and her/his name will be handled confidentially. Papers which are not connected to the topics of the journal could be rejected without reviewing.

Bewertung

Die Texte für das Oncothermia Journal werden durch die Redaktion kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden

Professor Dr. Peter Wust passed away.



Professor Dr. Peter Wust passed away on 9th July 2022. His death is an indescribable loss. Peter was full of strength and was a great tenure professor in the Department of Radiation Oncology and Radiotherapy at Charité University Medicine Berlin.

He has published valuable articles on the further development of oncological hyperthermia. His extensive knowledge and activities spanned radiation oncology, medical physics, and new applications of hyperthermia. We learned a lot from him. He was a good friend with solid morals.

His path was exemplary for us. We join in mourning. His life, teaching, and achievements will not be forgotten.

May you rest in peace.

We republish his obituary by Professor Dewhirst.

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39. ICHS Conference
It's time for prime time for oncologic hyperthermia/thermotherapy

Stephan Bodis[1], Oliver Riesterer[1], Emsad Puric[1], Niloy Datta[2]

[1]ITIS Foundation Zurich , University Hospital Zurich
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Cite this article as:
Bodis, S et al. (2022): 39. ICHS Conference - It's time for prime time for oncologic hyperthermia / thermotherapy

Oncothermia Journal 32, September 2022: 9 – 20,
http://www.oncotherm.com/sites/oncotherm/files/2022-09/Bodis_ICHS_Oncologic.pdf

SWISS HYPERTHERMIA NETWORK

39. ICHS Conference

It's time for prime time for oncologic hyperthermia / thermotherapy?

Stephan Bodis MD, Oliver Riesterer-1, Emsad Puric-1, Niloy Datta-2

ITIS Foundation Zurich, University Hospital Zurich*
RadioOnkologieZentrum Kantonsspital Aarau und Baden 1
Mahatma Gandhi Intitute, Sevagram, Wardha, Maharasthtra, India 2

1

SWISS HYPERTHERMIA NETWORK

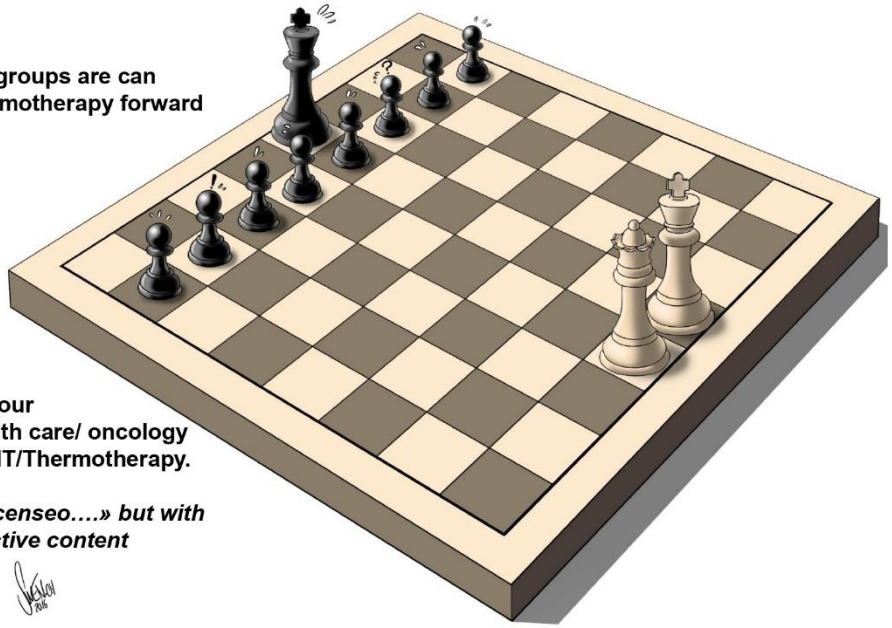
Conflicts of Interest Declaration

ElmediX - Member Advisory Board
ITIS Foundation - Member ITIS Foundation Board
Sensius - Member Thermotherapy Leadership Council

2

SWISS HYPERTHERMIA NETWORK

2 strong united leaders/groups are can push oncologic HT/Thermotherapy forward



Use discussions with your National leaders in health care/ oncology to promote oncologic HT/Thermotherapy.

Like Cesars «Ceterum censeo….» but with a positive and constructive content

SWISS HYPERTHERMIA NETWORK

How do we handle HT / TT in Switzerland ?

"Material and Methods of Thermotherapy (TT) within SHN"

SHN thermotherapy units are embedded within a Swiss Radiation Oncology

Use of superficial IR and RF and deep RF TT

Use of fractionated, moderate heated, regional TT

Planning "library" for specific tumors in defined anatomic regions

Experimental personalized (RT-like) planning selected for combined Proton-TT

Online temp. point measurements (at tumor and surrounding healthy tissue)

4

SWISS HYPERTHERMIA NETWORK

What is needed for prime time?

7 Bullet Points

1. **Need for evidence based medicine**
2. **Need for multicentric-prospective-randomised clinical trials**
3. **Need for Iso-certification for clinical thermotherapie units**
4. **Need for clinical European Research Networks**
5. **Need for re-imbursement for defined indications**
6. **Need for standardization of hard-software**
7. **Need for standardisation of patient workflow and QA**

5

Bullet point 1

Need for Evidence Based Medicine
2 slides

frontiers in Oncology

Datta et al.
June 2020

Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses

Nilay R. Datta[1]*, H. Petra Kok[2], Hans Crezee[2], Udo S. Gaipl[3] and Stephan Bodis[1]

[1]Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland
[2]Department of Radiation Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands
[3]Department of Radiation Oncology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Make your own SWOT analysis to push HT/TT

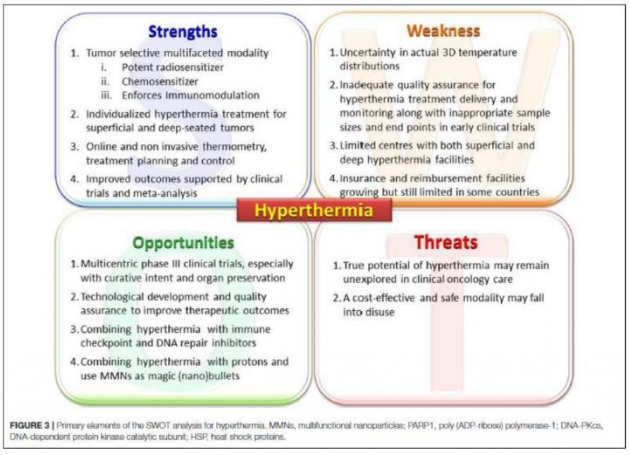
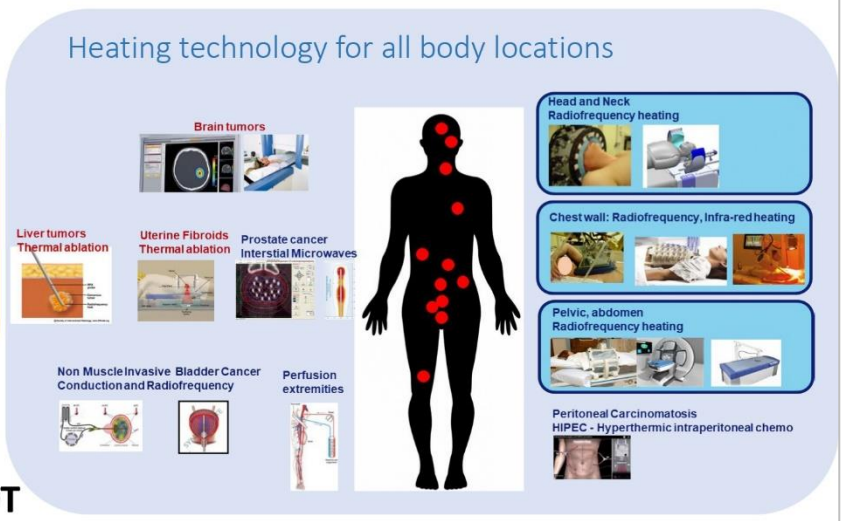


FIGURE 3 | Primary elements of the SWOT analysis for hyperthermia. MMNs, multifunctional nanoparticles; PARP1, poly (ADP-ribose) polymerase-1; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; HSP, heat shock proteins.

Strengths

1. Tumor selective multifaceted modality
   i. Potent radiosensitizer
   ii. Chemosensitizer
   iii. Enforces Immunomodulation
2. Individualized hyperthermia treatment for superficial and deep-seated tumors
3. Online and non invasive thermometry, treatment planning and control
4. Improved outcomes supported by clinical trials and meta-analysis



Make your own SWOT analysis to push HT/TT

*** Bullet point 2***

Need for multicentric prosp. rand. clinical trials
3 slides

Strengths

1. Tumor selective multifaceted modality
   i. Potent radiosensitizer
   ii. Chemosensitizer
   iii. Enforces Immunomodulation
2. Individualized hyperthermia treatment for superficial and deep-seated tumors
3. Online and non invasive thermometry, treatment planning and control
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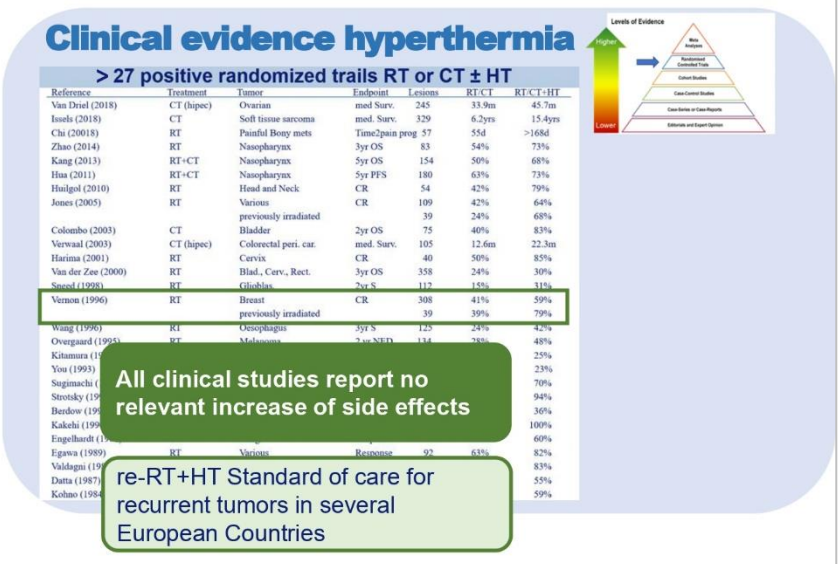
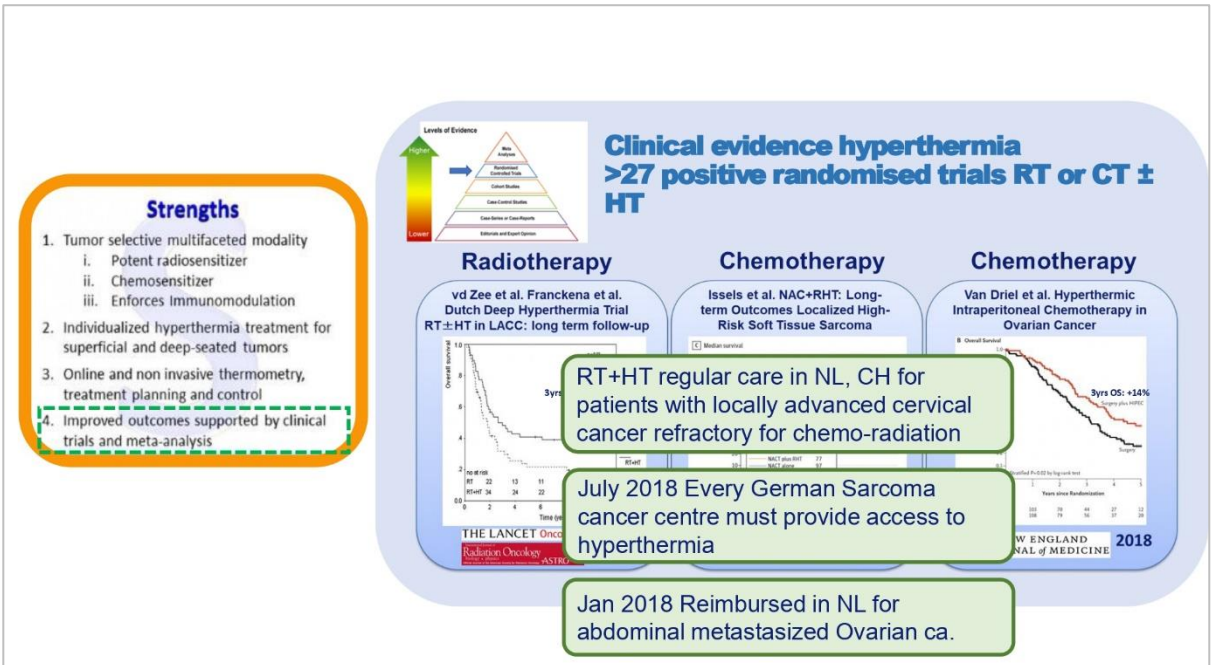


Reference	Treatment	Tumor	Endpoint	Lesions	RT/CT	RT/CT+HT
Van Driel (2018)	CT (hipec)	Ovarian	med Surv.	245	33.9m	45.7m
Issels (2018)	CT	Soft tissue sarcoma	med. Surv.	329	6.2yrs	15.4yrs
Chi (20018)	RT	Painful Bony mets	Time2pain prog	57	55d	>168d
Zhao (2014)	RT	Nasopharynx	3yr OS	83	54%	73%
Kang (2013)	RT+CT	Nasopharynx	5yr OS	154	50%	68%
Hua (2011)	RT+CT	Nasopharynx	5yr PFS	180	63%	73%
Huilgol (2010)	RT	Head and Neck	CR	54	42%	79%
Jones (2005)	RT	Various	CR	109	42%	64%
		previously irradiated		39	24%	68%
Colombo (2003)	CT	Bladder	2yr OS	75	40%	83%
Verwaal (2003)	CT (hipec)	Colorectal peri. car.	med. Surv.	105	12.6m	22.3m
Harima (2001)	RT	Cervix	CR	40	50%	85%
Van der Zee (2000)	RT	Blad., Cerv., Rect.	3yr OS	358	24%	30%
Snead (1998)	RT	Glioblas	2yr S	112	15%	31%
Vernon (1996)	RT	Breast	CR	308	41%	59%
		previously irradiated		39	39%	79%
Wang (1996)	RT	Oesophagus	3yr S	125	24%	42%
Overgaard (1995)	RT	Melanoma	2 yr NED	134	28%	48%
Kitamura (19						25%
You (1993)						23%
Sugimachi (						70%
Strotsky (19						94%
Berdow (19						36%
Kakehi (199						100%
Engelhardt (19						60%
Egawa (1989)	RT	Various	Response	92	63%	82%
Valdagni (19						83%
Datta (1987)						55%
Kohno (1984						59%



Phase III trials: Randomised, prospective, multicentric, standardised, international

Phase III trials with long term f/u and subsequent Metanalysis

- Critical for acceptance of TT/HT for stakeholders in oncology care, oncology politics, health care politics
- Critical for negotiations with national ministries of health care (They dont care about promising data)

(Also needed are Phase I / II trials)

...with an innovative potential for a better outcome, a better efficacy, better economics

Loco-regional moderate temperature HT/TT

- Proton Therapy, FLASH - RT
- Trimodality Therapy RT - Systemic Therapy - HT/TT
- Novel low budget RT and novel forms of Thermotherapy (also) for use in LMI countries

Local high temperature/ablative HT/TT

Whole body low to moderate HT/TT

- Oncologic setting combined with systemic therapy +/- RT
- Novel applications in medicine (E.g. multiresistant bacterial infections)

SWISS HYPERTHERMIA NETWORK

Bullet point 3

Need for Iso-Certification in clinical hyperthermia/thermotherapy units
1 slide

Comments from opinion leaders of our local tumor boards

- This was a good step for you
- We (start to) consider HT/TT now more seriously
- We understand now that you don't harm patients

ISO-Certification DIN EN ISO 9001:2015 of a Hyperthermia Unit in 2020 (Radiation Oncology Center Aarau and Baden)

Increased acceptance of TT/HT by hospital administrators and QA management


ClarCert

ZERTIFIKAT

Auf Grundlage der Zertifizierungsentscheidung vom 01.07.2020 bescheinigt die ClarCert GmbH, dass das

Kantonsspital Aarau

Tellstrasse 25, CH-5001 Aarau

für das

Radio-Onkologie-Zentrum KSA-KSB

für den Geltungsbereich

Anwendung der Hyperthermie

ein Qualitätsmanagementsystem nach

DIN EN ISO 9001:2015

erfolgreich eingeführt hat und anwendet.

Gültigkeitsdauer: 10.06.2021
Registrier-Nummer: ISO-091-3
Datum der Ausstellung: 30.07.2020
Neu-Ulm, den 30.07.2020

DAkkS

Dieses Zertifikat ist ein Unterzertifikat und nur in Verbindung mit dem Hauptzertifikat mit der Registriernummer ISO-091-3 gültig.

Jürgen Fischer
Geschäftsführer ClarCert GmbH

ClarCert GmbH · Gartenstraße 24 · D-89231 Neu-Ulm

SWISS HYPERTHERMIA NETWORK

Bullet point 4

Need for International HT/TT Research Networks
3 slides

Current SHN activities within intl. networks

2019 ESHO Workshop to promote/endorse European clinical trials:

- Need for international multicentric clinical trials in oncology for Hyperthermia combined with Radiotherapy (endorsed by ESHO)

- F/u meeting and joining forces between the ESHO Clinical Trial Comittee and the Atzelsberg Group form Germany

EU Horizon 2020 Grant H2020-MSCA-ITN-2020-955625 (The EU Research and Innovation Framework Programme)

- Hyperthermia boosting the effect of radiotherapy

ESTRO 2021

Interdisciplinary Symposium in Oncologic Hyperthermia: A session jointly with leaders from Europe, Japan and USA

Current status of hyperthermia in radiation oncology

CANCERS 2022 (IF > 6)

Special issue dedicated to Oncologic Thermo-Radiotherapy

HYPERBOOST

Hyperthermia boosting the effect of Radiotherapy

H2020-MSCA-ITN-2020-955625

6 countries
11 beneficiaries
14 PhD students
Budget: € 4 million

Project coordination:
Hans Crezee
Amsterdam UMC

ESTRO 2021

Joint ESTRO-JASTRO Hyperthermia Symposium

Current status of hyperthermia in radiation oncology

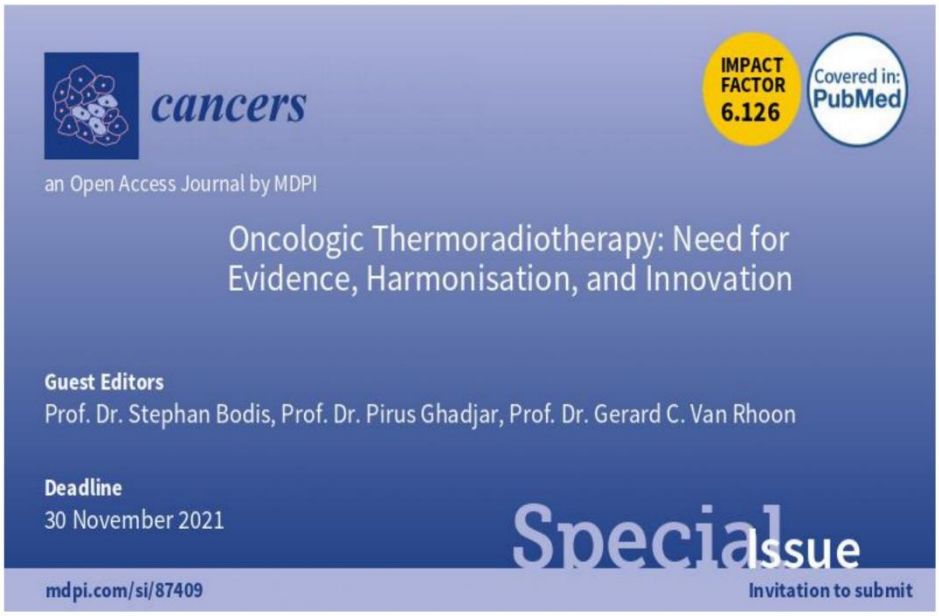
Biological rational for combining heat and radiation
Jens Overgaard DK

Clinical heating techniques, thermometry and quality assurance
Hans Creeze NL

Status of clincial Hyperthermia in Japan
Hideyuki Sakurai Jp

Thermoradiotherapy: Clinical evidence and potential indications
Zeljko Vujaskovic USA

Conclusions by the ESTRO President
Ben Slotman NL



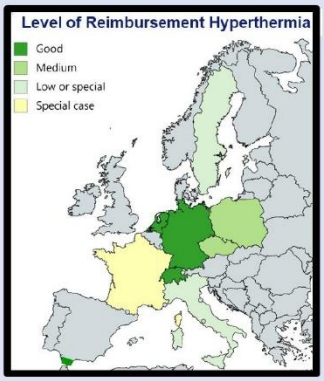
Bullet point 5

Need for re-imbursement for defined indications
2 slides

Weakness

1. Uncertainty in actual 3D temperature distributions
2. Inadequate quality assurance for hyperthermia treatment delivery and monitoring along with inappropriate sample sizes and end points in early clinical trials
3. Limited centres with both superficial and deep hyperthermia facilities
4. Insurance and reimbursement facilities growing but still limited in some countries

Reimbursement hyperthermia



Netherlands: HT reimbursed with radiotherapy. Regional deep and superficial hyperthermia, from January 1st 2010 onwards:

- **Locally advanced cervical cancer for patients that are refusing or refractory for chemoradiation**

Any recurrent tumor in previously irradiated areas:

- **breast ca.**
- **lymph node metastasis of Head & Neck ca.**
- **tumors causing local complaints as palliation**
- **Rectum ca.**
- **Superficial local recurrence of mesothelioma**
- **Lymph node met's or recurrent malig. melanoma**

Hyperthermic Intraperitoneal Chemotherapy:

- **Peritoneal metastasis colon ca, mesothelioma**
- **Since 2019: ovarian ca.**

SWISS HYPERTHERMIA NETWORK

Status reimbursement Thermotherapy in CH (only combined TT + RT) in 2021

4 indications for superficial HT approved 2016 (unlimited)

Curative: Recurrent Melanoma, H/N recurrences (Pre-RT), Chest wall BC recurrences (Pre-RT)

Palliative: Local tumor recurrence with compression symptoms

2 indications for deep HT approved 2021 (unlimited)

Curative: Cervix Cancer if contraindication for concurrent CT-RT

Palliative: Painfull bone metastases of spine and pelvis

2 indications approved (limited 2021-2023)

Curative Soft Tissues Sarcomas (To preserve anatomical functionality) only in clinical trials (incl. protontherapy!)

Palliative: Local tumor recurrence with compression symptoms

All indications restricted to synchronous RT and HT/TT

All patients must be presented and discussed @ the local tumorbord of an accredited oncology center

Hyperthermia/Thermotherapy Center must be an accredited member of the Swiss Hyperthermia Network

Bullet point 6

Need for standardisation of all clinically used hard-software
2 slides

Opportunities

1. Multicentric phase III clinical trials, especially with curative intent and organ preservation
2. Technological development and quality assurance to improve therapeutic outcomes
3. Combining hyperthermia with immune checkpoint and DNA repair inhibitors
4. Combining hyperthermia with protons and use MMNs as magic (nano)bullets

Non-invasive thermometry by MRI research

- Munich
- Rotterdam
- Dusseldorf
- Tubingen
- Erlangen

A new software ?

We need a standardisation of our HT/TT vocabulary

We need a glossary/encyclopedia dedicated to HT/TT (in progress by ESHO)

- We should harmonise our technical terms
- We should harmonise our keywords
- We should create new and commonly accepted terms where needed

Crucial for the promotion a global HT/TT «language» understood and accepted by all stakeholders including our patients and their families

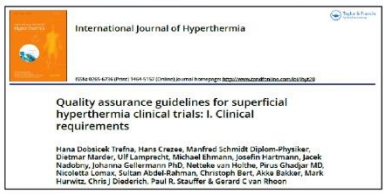
Only possible with a joint effort between science and industry
(including all major societies dedicated to oncology HT/TT)

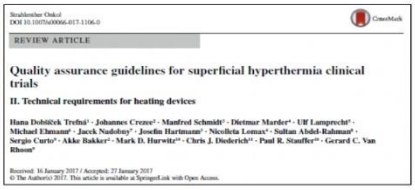
Bullet point 7

Need for standardisation of workflow and QA
1 slides and discussion

ESHO technical committee guidelines (lead - guidelines)

Superficial HT - Current guideline 2017





Deep HT - Current guideline 2012

New release 2021

Coordination with industry/manufacturer standards
Coordinaton with national guidelines
Coordination with ISO-certifications

SWISS HYPERTHERMIA NETWORK

As an oncologic «underdog»
And with a strategy and a vision
All we should care is

- Evidence and Empathy
- Quality- and Outcome Analysis
- Cooperation and Communication

and thereby push HT/TT into prime time

21

If we join forces it might be a good time for prime time
for hyperthermia/thermotherapy

Thank you for your attention

Update on mEHTGlio phase III trial. First results and comments.

Elisabeth Arrojo[1], Paola Navarrete[1] , Uriel Corro[1]

[1]University Hospital Marques de Valdecilla, Santander, Spain

Cite this article as:
Arrojo, E. et al. (2022): Update on mEHTGlio phase III trial. First results and comments

Oncothermia Journal 32, September 2022: 21 – 35,
http://www.oncotherm.com/sites/oncotherm/files/2022-09/Arrojo_ICHS_Update-on-mEHTGlio.pdf

UPDATE ON mEHTGLIO PHASE III TRIAL. FIRST RESULTS AND COMMENTS

Elisabeth Arrojo[1], Paola Navarrete[1], Uriel Corro[1].
[1]University Hospital Marques de Valdecilla, Santander, Spain

Elisabeth Arrojo Álvarez, MD, PhD

Radiation Oncologist at University Hospital Marqués de Valdecilla
Medical director at INMOA (Medical Institute of advanced oncology)
ICHS President

INTRODUCTION…

University Hospital Marqués de Valdecilla

Santander, Spain

Radiotherapy department:

- Team: 62 people.
  - 11 Radiation oncologists.
- External beam radiotherapy:
  - 3 linear accelerators:
    - Radiosurgery
    - Stereotactic RT (intra and extracraneal)
    - Image guided RT
    - Intensity modulated RT
- 2 operating rooms for Brachytherapy
  - HDR and LDR

University Hospital Marqués de Valdecilla

- **The first public** hospital in **Spain** with a **mEHT** device.
- **The first public** hospital in **Spain** which will have protontherapy.

Virtual Hospital Valdecilla

- A **pioneer center in Europe** in the use of **clinical simulation for the training** of health professionals and the improvement of patient safety.
- Works in **collaboration with the Center for Medical Simulation** (Boston)

IDIVAL Research Institute

In March 2015 IDIVAL was awarded by the Spanish Institute of Health Carlos III as **one of the reference Institutes for Health Research in Spain**

Valdecilla
Hospital Universitario Marqués de Valdecilla

mEHT at Valdecilla Hospital

- Since July 2019

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Valdecilla
Hospital Universitario Marqués de Valdecilla

Medical Institute of advanced oncology
INMOA - Madrid

Hyperthermia at private practice...

- 3 mEHT devices

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Hospital Universitario Marqués de Valdecilla

ESMO OPEN | CANCER HORIZONS

ORIGINAL RESEARCH | VOLUME 6, ISSUE 3, 100157, JUNE 01, 2021

Impact of the COVID-19 pandemic on the care of cancer patients in Spain

M. Amador • X. Matias-Guiu • G. Sancho-Pardo • ... R. García-Sanz • Á. Rodríguez-Lescure • L. Paz-Ares • Show all authors

Open Access • Published: May 17, 2021 • DOI: https://doi.org/10.1016/j.esmoop.2021.100157 •

Check for updates

Highlights

- The number of new cancer patients decreased 20.8%
- Assistance protocols were adapted
- Inclusion in clinical trials decreased by 12.9%

mEHT at Valdecilla Hospital

- Stopped for 18 months

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Valdecilla
Hospital Universitario Marqués de Valdecilla

Hungary 28-29 September, 2018

ICHS
36th Conference of the International Clinical Hyperthermia Society

Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)

Elisabeth E. Arrojo, MD, PhD
Radiation Oncologist
University Hospital Marqués de Valdecilla, Santander, Spain

Valdecilla
Hospital Universitario Marqués de Valdecilla

INMOA
INSTITUTO MÉDICO DE ONCOLOGÍA AVANZADA

What happened with that phase III trial called mEHTGlio for GBM treated with mEHT which started 2 years ago…?

1.1 **Title: "Treatment with modulated electro-hyperthermia in high grade gliomas (grade III and IV) as an adjuvant treatment to standard radiotherapy and chemotherapy or as a unique treatment".**

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Valdecilla
Hospital Universitario Marqués de Valdecilla

What happened with that phase III trial called mEHTGlio?

- **We tend to think the results are not good if we don't have results…**

1.1 Title: "Treatment with modulated electro-hyperthermia in high grade gliomas (grade III and IV) as an adjuvant treatment to standard radiotherapy and chemotherapy or as a unique treatment".

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Valdecilla Hospital Universitario Marqués de Valdecilla

What happened with that phase III trial?

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Let's remind...

5. STUDY DESIGN

This is a prospective, randomized study designed to evaluate the possible benefit in terms of better control of the disease, of adding a treatment with modulated electrohyperthermia to standard surgery, radio and chemotherapy treatments or as a single treatment in those cases that meet the inclusion criteria of the study and in which it is not possible to apply any other treatment.

It is hypothesized that treatment with modulated electrohyperthermia, will produce different beneficial effects that will impact on better oncological control such as:

- Radiosensitivity: mEHT will increase oxygenation and therefore will decrease hipoxia, improving this way radiosensitivity in those patients who will receive radiotherapy treatment concomitantly with mEHT.
- Chemosensitivity: mEHT will increase oxygenation and improve blood flow to improve the "drugs" distribution in the tumor area.
- Improve cancer cell killing: mEHT will promote cancer cell destruction through apoptosis by a mechanism of selection and modulation.

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mEHTGlio trial: Inclusion criteria

HIGH GRADE GLIOMA
Patients able to understand and sign informed consent
Age >18 years
Karnofsky ≥ 70
• Confirmed by pathology High Grade Glioma (III and IV) • Newly diagnosed patients • Patients with relapse/progression.

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Valdecilla

Update on mEHTglio phase III trial. First results and comments

- Patients diagnosed with WHO grade III/IV glioma at University Hospital Marques of Valdecilla were recruited in phase III mEHTGlio trial between August 2019 and March 2021.

- Due to COVID19's pandemic and technical reasons recruitment was **stopped for 18 months during this period**.

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Valdecilla

Update on mEHTglio phase III trial. First results and comments

- Arm 1: Patients at first diagnosis randomized to:
  - Control group: Standard treatment (temozolamide + radiotherapy)
  - Experimental group: Standard treatment
    + mEHT:
    - 5 times a week (30 minutes before radiotherapy).
    - One hour treatment
    - Power between 45 and 60W.
- Arm 2: Patients with progression after standard treatment, treated with mEHT in monotherapy or concomitant with CT.
  - mEHT:
    - 3 times a week.
    - One hour treatment
    - Power between 45 and 60W.

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Valdecilla

RESULTS

- Due to COVID19's pandemic and technical reasons recruitment was **stopped for 18 months during this period.**
  - 26 patients were recruited.

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Valdecilla Hospital Universitario Marqués de Valdecilla

Arm 1: Randomized:

Control group: Standard treatment vs

Experimental group: Standard treatment+mEHT.

- 14 patients:
  - 8 patients randomized to Experimental group
  - 6 patients randomized to control group
- 4 patients were excluded for this report:
  - 3 did not begin/complete treatment (2E and 1C group).
  - 1 was a grade III glioma (E group). Due to the low number of patients recruited and in order to make more comparable groups the grade III patient was excluded.

ARM 1	EXPERIMENTAL	CONTROL
N (Patients evaluated)	5	5
Average Age	53	61
IDH Status	17% Positive (n=1)	17% Positive (n=1)
Average Follow-Up	22,09 months (8,8-28,4)	27,99 months (22,10-30,4)

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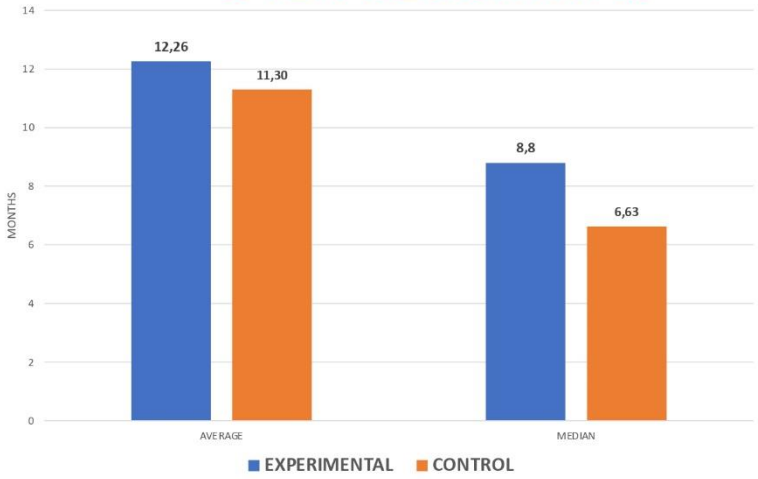
OVERALL SURVIVAL



- FU exp: 22 months
- FU control: 27,99 monts

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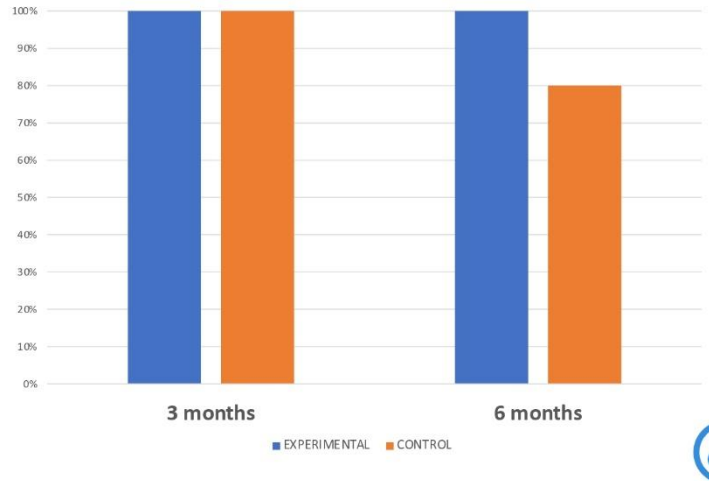
OVERALL SURVIVAL



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Arm 2: Patients under progression after ST, treated with mEHT in monotherapy or concomitant with CT.

- 12 patients recruited
  - 2 patients did not complete treament because of very advanced disease.
  - 2 patients treated in monotherapy showed no response (very advanced tumor. Limited Karnofsky).
  - 8 patients treated with mEHT + chemotherapy.

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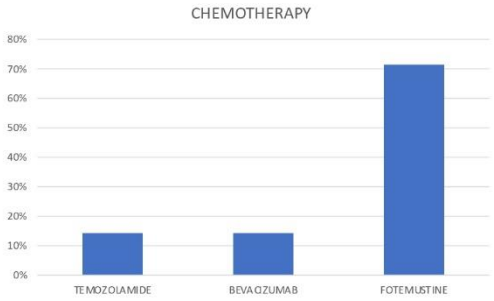
Arm 2: Patients with progression after ST, treated with mEHT concomitant with CT.



- N= 8
  - 50% progressed
  - 50% responded (4 patients)
    - 2 treated with Fotemustine:
      - 1 alive after 7 months and showing good response.
      - 1 died 7 months after beginning mEHT
    - 1 treated with Bevacizumab died 6 months after beginning mEHT
    - 1 treated with Temozolamide died 6,4 months after beginning mEHT

All but one: 4 weeks treatment → wait 8 weeks for MRI → if Ok → 4 weeks treatment → and so on..

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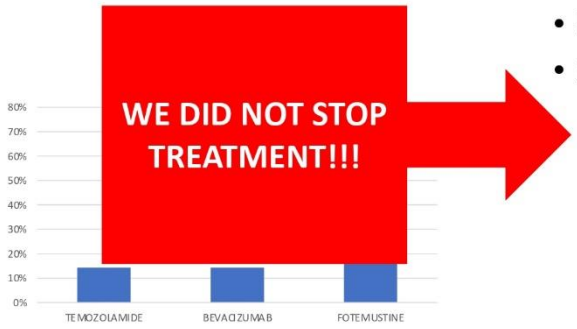
CONCERN!

- One feeling…
  - Patients progress mainly when we stop treatment?
    - "Feeling" from the trial at Public hospital and experience outside the trial at private practice…

- (• 3 mEHT devices

…here.
…ways" there?

Arm 2: Patients with progression after ST, treated with mEHT concomitant with CT.



- 50% progressed
- 50% resp… (4 patient…)
  - 2 …eated with Fotemustine:
    - **1 alive after 7 months and showing good response.**
    - 1 died 7 months aft… …ginning …
  - 1 treated with Bevacizumab died 6 months after beginning mEHT
  - 1 treated with Temozolamide died 6,4 months after beginning mEHT

CONCERN!

- Patients progress mainly when we stop treatment?
- Glioblastoma is ALWAYS there.
  - Treatment should be always there?

- **We are thinking about changing trial's protocol in order to go on with treatment until progression.**

Toxicities

- Minor toxicities: <5% light headache for less than 1 hour.
- No epileptic seizures.
- **No** grade III or IV toxicities.

CONCLUSIONS:

- These are the first preliminary results from a phase III trial comparing ST vs ST+mEHT in patients diagnosed with high grade glioma.
- We don't have conclusions…
  - … Yet
- COVID19 pandemic has delave[d] **we don't have enough number of patients to ri[se]** h groups seem to be comparable and the[re] er results regarding overall survival.
- Adding mEHT to RT/C[T] toxicities.
- **More patients and follo[w] needed to rise conclusions.**

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Valdecilla Hospital Universitario Marqués de Valdecilla

ICHS 39.

39th Conference of the International Clinical Hyperthermia Society

5 November, 2021

You still have to come to Spain!!!

Thank you!

earrojo@inmoa.es

INMOA INSTITUTO MÉDICO DE ONCOLOGÍA AVANZADA

Valdecilla Hospital Universitario Marqués de Valdecilla

An overview of Oncothermia as a treatment modality for cervical cancer

Carrie Minnaar [1,2], Jeffrey Kotzen [1,2]

[1] University of Witwatersrand, South Africa
[2] Wits Donald Gordon Academic Hospital, South Africa

Cite this article as:
Minnaar C.A. et al. (2022): An overview of Oncothermia as a treatment modality for cervical cancer

Oncothermia Journal 32, September 2022: 36 – 49,
http://www.oncotherm.com/sites/oncotherm/files/2022-09/Minnaar_ICHS_Overview_of_Oncothermia.pdf

An overview of Oncothermia as a treatment modality for cervical cancer

Minnaar C.A.[1,2] Kotzen J.A.[1,2]

[1] University of Witwatersrand, South Africa
[2] Wits Donald Gordon Academic Hospital, South Africa

Disclosures:

The authors do not have any conflicts of interest to declare.

Introduction:

Modulated electro-hyperthermia (mEHT); Oncothermia™

- **Mild** heating
- **Capacitive-coupled** set-up
- **Amplitude modulated** 13.56MHz radiofrequency waves

- **Cervical cancer** and the **treatments:**
- Significant morbidity and
- Negatively impacts the Quality of Life (QoL) of patients

Introduction:

1. We **summarise the literature** on mEHT for the management of cervical cancer
2. Describe a **cost effectiveness analysis** (CEA) on mEHT for the management of locally advanced cervical cancer (LACC),
3. Report **preliminary three year survival data** from the ongoing randomised controlled Phase III trial on mEHT plus chemoradiotherapy (CRT) in South Africa (SA).

Methodology:

Review:

- A literature search for "hyperthermia", "modulated electro-hyperthermia", and "Oncothermia" in "oncology", and "cervical cancer" was conducted.
- Studies that did not utilise mEHT were excluded. All papers on mEHT used for the management of cervical cancer were included.

Three Year Survival:

- Data from the ongoing LACC SA trial were used to evaluated three year survival for patients treated with mEHT plus CRT.

Methodology:

CEA:

- Cost analysis for **RT** with/without mEHT for LACC
- Report from **2012**
- Time horizon: **3 years**
- Perspective: **3rd party payer**
- **Markov** model, with **6 months cycle** length
- Data: 3 year data from the **Dutch Deep HT trial** [1], extrapolated into the South African setting, using mEHT costs.
- Costs are reported in SA Rands.
- Considered direct medical costs only
- Primary outcome: Cost per Quality Adjusted Life Year (**QALY**).

Methodology:

CEA:

- Cost analysis for **CRT** with/without mEHT for LACC
- Preliminary 2021 results
- Time horizon: **3 years**
- Perspective: **Private Healthcare** and **Public Healthcare**
- **Markov** model, with **6 months cycle** length
- Data: 3 year data from the **mEHT LACC SA** study
- Costs are reported in SA Rands.
- Considered direct medical costs only
- Primary outcome: Cost per Quality Adjusted Life Year (**QALY**).

Results: mEHT- Temp&Blood flow

20 patients with cervical cancer were treated with mEHT

Measurements

- **Temp**: Peri-tumour using an internal organ temperature probe
- **Blood flow**: 3D colour Doppler ultrasound used to determine peak systolic velocity end diastolic velocity ratio *(SID* ratio) and the resistance index (RI) within blood vessels.

Results:

- **Temp:** mean peri-tumour temperature
  - Baseline: 36.7 ± 0.2 °C
  - 30 minutes: 37.5 ± 0.5 °C
  - 60 minutes: 38.5 ± 0.8 °C
- **Blood flow**,
  - *mEHT = significant increase in tumour blood flow*

Lee S-Y, *et al,* **The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma**. *International Journal of Hyperthermia*. 2018;34(7):953-960.

Results: mEHT + Chemotherapy

- 2017 Lee *et al.(2017)*
- Randomised trial: mEHT+ChT vs ChT alone for **previously irradiated residual/locally recurrent cervical cancer**
- Incl. loco-regional metastases
- mEHT: **3/wk** →**36** treatments, Power: 80→**150**W, **60** minutes
- ChT: platinum based

Group	TP (cycle)	TC (cycle)	FP (cycle)	Cisplatin (cycle)
Cht (n=20)	8 (5-7)	6 (6-9)	6 (4-6)	0
ChT+mEHT (n=18)	6 (5-6)	4 (6)	6 (4-6)	2 (5-6)

TP, paclitaxel+cisplatin; TC, paclitaxel+carboplatin; FP, cisplatin+5-fluorouracil.

Results: mEHT + Chemotherapy

- **Overall response significantly better in mEHT group**
- mEHT did not result in any differences in treatment toxicity

Clinical response following completion of treatment.

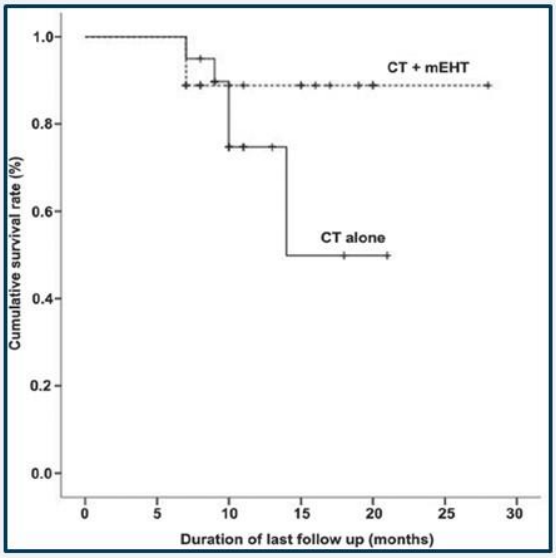
Group	CR	PR	SD	PD	P value
Cht (n=20)	4	3	1	12	*p= 0.0461*
ChT+ mEHT (n=18)	9	2	2	5	

Clinical response at last follow up

Group	CR	PR	SD	PD	P value
Cht (n=20)	4	3	1	12	*p= 0.0218*
ChT+ mEHT (n=18)	9	2	2	5	

Results: mEHT + Chemotherapy

- No significant difference in survival



Overall survival.
ChT +mEHT did not significantly increase the overall survival rate (p=0.235).

Lee S, *et al* **Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation.** *Oncology Letters*. 2017;14(1):73-78.

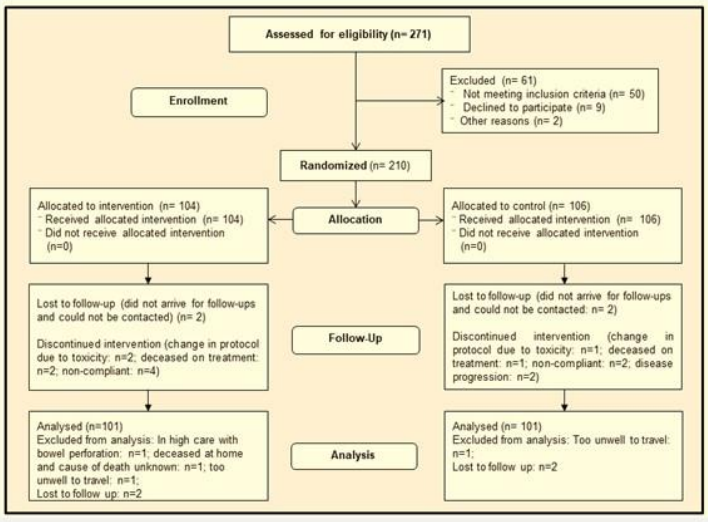
Results: mEHT + Chemoradiotherapy

mEHT LACC SA trial:

- FIGO stage IIB-IIIB;
- HIV +/-;
- CRT with radical intent;
- Signed informed consent

Protocol:

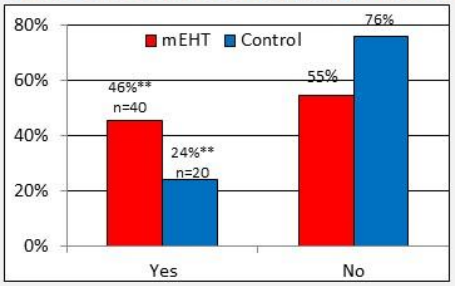
- mEHT:
  - 2/wk, total 10
  - immediately before EBRT
  - 55 minutes,
  - starting at 60W →130W
- Radiation:
  - 50Gy EBRT in 25#
  - 3x 8Gy HDR Brachytherapy
- Chemotherapy:
  - 2x Cisplatin: 80mg/m2



Results: mEHT + Chemoradiotherapy

- Improved LDC with the addition of mEHT to CRT [4]
- Without any significant effect on early toxicity [5].
- With a quality of life (QoL) benefit [5]

LDC at 6 months in Surviving Patients



mEHT Group:
n=88
[87% survival]
46% LDC

Control Group:
n=83
[82% survival];
24% LDC

Chi2: ***p=0.003***

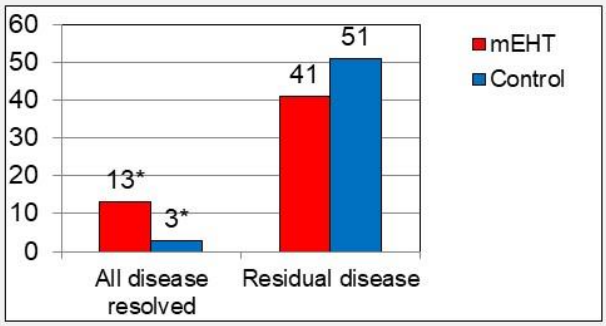
Pain, emotional well-being, and physical function, were significantly higher in mEHT group (EORTC)

	LDFS 6 months	LDC 6 months	CMR
mEHT	n=39/101 [39%]	n=40/88 [46%]	n=49/85 [59%]
Control	n=20/101 [20%]	n=20/83 [24%]	n=26/73 [36%]
p	OR: 0.36, 95% CI: 0.19-0.69; *p=0.002*	OR: 0.39, 95% CI: 0.20-0.77; *p=0.006*	Fischer's exact *p=0.005*

Results: mEHT + Chemoradiotherapy

Abscopal effect: in participants in whom extra-pelvic nodal disease was visualized on the pre-treatment ^{18}F-FDG PET/CT studies [6]

Confirming the immune-modulating effects of mEHT described in pre-clinical studies.



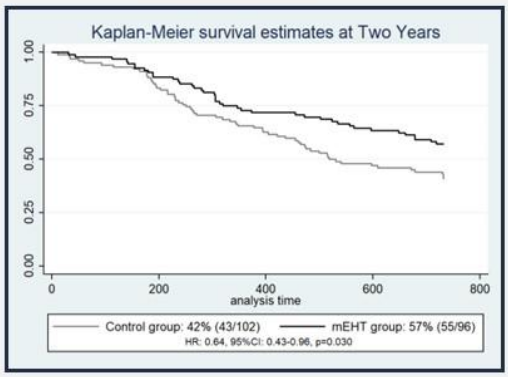
In a multivariate analysis, Age, Number of cisplatin doses, Total RT dose, Days between last RT and PET/CT, **were not associated with an abscopal effect.** In a univariate analysis, CD4 count was also not predictive of an abscopal effect.

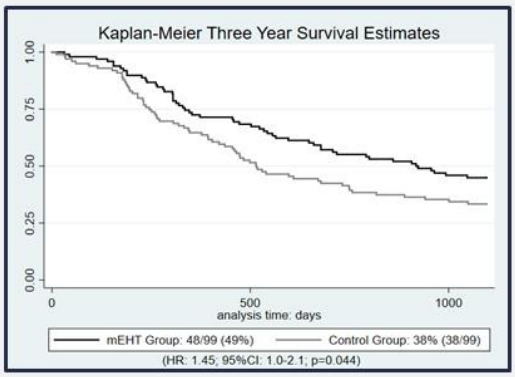
Results: mEHT + Chemoradiotherapy

Three Year Results:

3yr all mortality survival and DFS is significantly more likely in the mEHT group
mEHT did not result in any significant changes in late toxicity

	2YR OS	3YRS OS	DF at 3YRS
mEHT	n=55/96 [57%]	n=48/98 [49%]	n=33/98 [34%]
Control	n=43/102 [42%]	n=38/99 [38%]	n=14/99 [14%]
P value	HR: 0.64, 95% CI: 0.43-0.96, *p=0.030*	HR: 1.45; 95% CI: 1.0-2.1; *p=0.044*	OR:2.4; 95% CI: 1.3-4.4; *p=0.003*





Results: CEA

mEHT + RT

- **Addition of mEHT to RT dominated treatment by RT alone**
- The **addition of mEHT** was **less costly** and **more effective**.
- Driven by the difference in progression free survival (high costs of progressive disease)
- ***There is a 100% probability that the cost of combination treatment is less than that of radiation* therapy.**

Results: CEA

mEHT + CRT

- Markov Cost Effectiveness model assumes that patients start progression free and then enter the model. Once in the model, there are three different mutually exclusive states into which patients will move:
  - Progression free survival
  - Progression
  - Death
- Patients incur treatment costs during the first cycle and the other costs as they progress.

Results: CEA

mEHT + CRT

Public Healthcare Perspective:

- mEHT+CRT **DOMINATES** the CRT
- More health benefits at lower costs
- The probability that mEHT+CRT is cost-effective compared with CRT only treatment is about 82.2% at No additional cost

Results: CEA

mEHT + CRT

Private Healthcare Perspective:

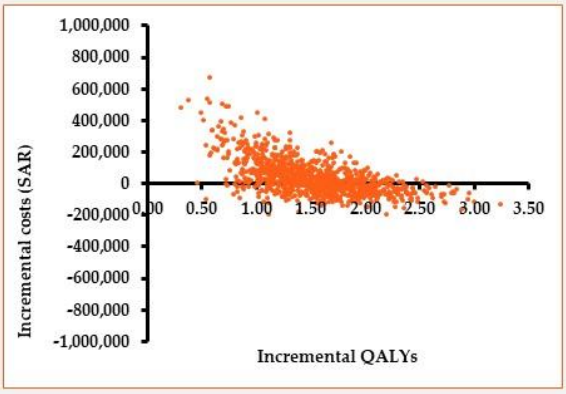
- mEHT+CRT **DOMINATES** the CRT
- More health benefits at lower costs
- The probability that mEHT+CRT is cost-effective compared with CRT only treatment is about 77.7% at No additional cost

Results: CEA

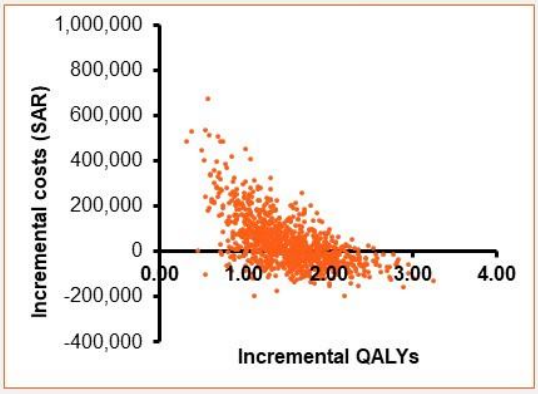
mEHT + CRT

ICER planes show mEHT+CRT = more health effects at a less cost over 3-years (mEHT dominant)

Public Healthcare Perspective:



Private Healthcare Perspective:



Conclusion:

- mEHT combined +ChT for the management of residual or recurrent disease significantly improves local disease response in these patients.
- mEHT +CRT significantly improves:
  - LDC, 3 year survival, 3 year DFS
  - without increasing the toxicity profile

Addition of mEHT to CRT for LACC is more effective and less costly

Future Perspective:

- Following the review, we recommend mEHT be included in the guidelines for the management of LACC and recurrent/residual cervical cancer.
- Consideration should be given to developing studies on **mEHT + immunotherapy**
- A **CEA analysis** of mEHT plus CRT using the new three year survival data is underway.

Acknowledgements

- Dr. Innocent Maposa: Biostatistician from the Bioethics Department at the University of the Witwatersrand and Faculty of Health Sciences
- The staff at the CMJAH who have been invovled int eh care of the patients
- The patients, without whom this research would not have been possible – they fight continuously, and bravely, despite the many challenges that face on a daily basis
- Oncotherm: supplied the EHY 2000 Plus for research purposes
- Funding was obtained from the National Research Foundation of South Africa

Thank you

References:

1. Van Der Zee J, González González D. The Dutch Deep Hyperthermia trial: Results in cervical cancer. *International Journal of Hyperthermia*. 2002;18(1):1-12.
2. Lee S, Lee N, Cho D, Kim J. Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. *Oncology Letters*. 2017;14(1):73-78.
3. Lee S-Y, Kim J-H, Han Y-H, Cho D-H. The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma. *International Journal of Hyperthermia*. 2018;34(7):953-960.
4. Minnaar CA, Kotzen JA, Ayeni OA, et al. The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial. *PLoS ONE*. 2019;14(6):1-23.
5. Minnaar CA, Kotzen JA, Naidoo T, et al. Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients. *International Journal of Hyperthermia*. 2020;37(1):263-272.
6. Minnaar CA, Kotzen JA, Ayeni OA, Vangu M, Baeyens A. Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients. *Frontiers in Oncolgy*. 2020;10:Article 376.

Results: mEHT

- The following parameters were documented for the
- tumour area:
  - The ratio of peak systolic velocity to end-diastolic velocity
  - *(SID* ratio) of intra-tumoural vessels
  - The resistance index (RI) of intra-tumoural vessels
  - The RI in tumour-supplying vessels
  - The RI was calculated according to the following equation: RI= (peak systolic velocity - end-diastolic velocity)/peak systolic velocity

SID and RI significantly increased post treatment.

Multimodal immunotherapy with IO-Vac® for patients with GBM: a single institution experience

Stefan W. Van Gool [1,]

[1] on behalf of the IOZK Team
www.iozk.de

Cite this article as:
Van Gool S.W (2022): Multimodal immunotherapy with IO-Vac® for patients with GBM: a single institution experience

Oncothermia Journal 32, September 2022: 50 – 61,
http://www.oncotherm.com/sites/oncotherm/files/2022-09/Van_Gool_ICHS_Multimodal.pdf

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

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IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Standard of care; Stupp 2005, 2009
Neurosurgery + radiochemotherapy + chemotherapy

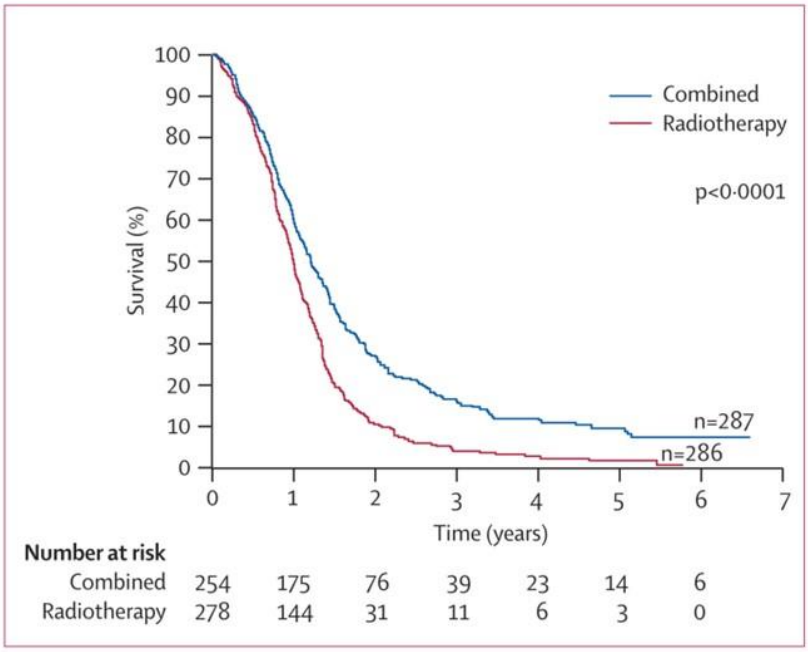


Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

1

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

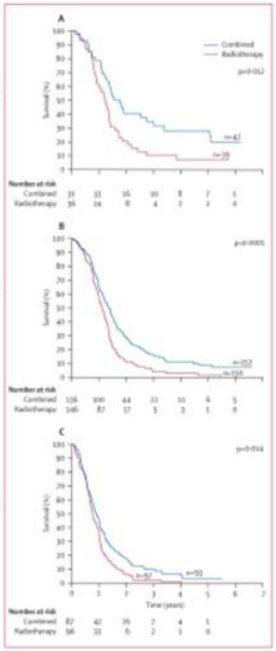
Standard of care; Stupp 2005, 2009
Neurosurgery + radiochemotherapy + chemotherapy

Stratification in randomization
WHO performance; Extent of resection; Treatment center

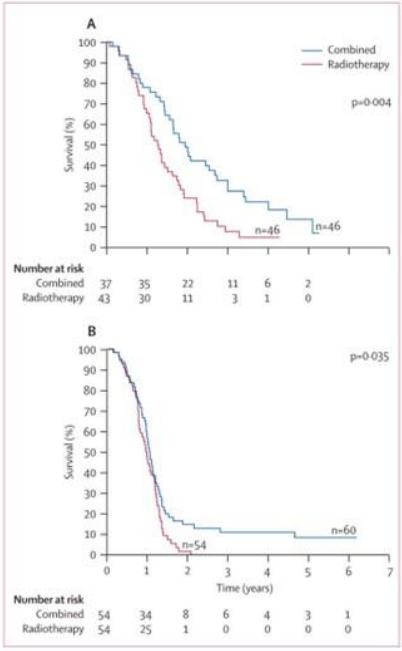
RPA3

RPA4

RPA5



Post-hoc Subgroup analysis
MGMT promoter methylation status



Phase I / phase II trials; DC vaccination for GBM

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1. Liau LM, Black KL, Martin NA, et al. Treatment of a patient by vaccination with autologous dendritic cells pulsed with allogeneic major histocompatibility complex class I-matched tumor peptides. Case Report. Neurosurg Focus 2000;9:e8.
2. Yu JS, Wheeler CJ, Zeltzer PM, et al. Vaccination of malignant glioma patients with peptide-pulsed dendritic cells elicits systemic cytotoxicity and intracranial T-cell infiltration. Cancer Res 2001;61:842-7.
3. Kikuchi T, Akasaki Y, Irie M, Homma S, Abe T, Ohno T. Results of a phase I clinical trial of vaccination of glioma patients with fusions of dendritic and glioma cells. Cancer Immunol Immunother 2001;50:337-44.
4. Wheeler CJ, Black KL, Liu G, et al. Thymic CD8+ T cell production strongly influences tumor antigen recognition and age-dependent glioma mortality. J Immunol 2003; 171:4927-33.
5. Yamanaka R, Abe T, Yajima N, et al. Vaccination of recurrent glioma patients with tumour lysate-pulsed dendritic cells elicits immune responses: results of a clinical phase I/II trial. Br J Cancer 2003;89:1172-9.
6. Caruso DA, Orme LM, Neale AM, et al. Results of a phase 1 study utilizing monocyte-derived dendritic cells pulsed with tumor RNA in children and young adults with brain cancer. Neuro Oncol 2004;6:236-46.
7. De Vleeschouwer S, Van Calenbergh F, Demaerel P, et al. Transient local response and persistent tumor control of recurrent malignant glioma treated with combination therapy including dendritic cell therapy. J Neurosurg (pediatrics) 2004;100:492-7.
8. Kikuchi T, Akasaki Y, Abe T, et al. Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. J Immunother 2004;27:452-9.
9. Rutkowski S, De Vleeschouwer S, Kaempgen E, et al. Surgery and adjuvant dendritic cell-based tumour vaccination for patients with relapsed malignant glioma, a feasibility study. Br J Cancer 2004;91:1656-62.
10. Wheeler CJ, Das A, Liu G, Yu JS, Black KL. Clinical responsiveness of glioblastoma multiforme to chemotherapy after vaccination. Clin Cancer Res 2004;10:5316-26.
11. Yu JS, Liu G, Ying H, Yong WH, Black KL, Wheeler CJ. Vaccination with tumor lysate-pulsed dendritic cells elicits antigen-specific, cytotoxic T-cells in patients with malignant glioma. Cancer Res 2004;64:4973-9.
12. Liau LM, Prins RM, Kiertscher SM, et al. Dendritic cell vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local central nervous system tumor microenvironment. Clin Cancer Res 2005;11:5515-25.
13. Yamanaka R, Homma J, Tsuchiya N, Yajima N, Kobayashi T, Tanaka R. Tumor lysate and IL-18-loaded dendritic cells elicits Th1 response, tumor-specific CD8+ cytotoxic T cells in patients with malignant glioma. J Neurooncol 2005;72:107-13.
14. Yamanaka R, Homma J, Yajima N, et al. Clinical evaluation of dendritic cell vaccination for patients with recurrent glioma: results of a clinical phase I/II trial. Clin Cancer Res 2005;11:4160-7.
15. Khan JA, Yaqin S. Dendritic cell therapy with improved outcome in glioma multiforme--a case report. J Zhejiang Univ Sci B 2006;7:114-7.
16. Okada H, Lieberman FS, Walter KA, et al. Autologous glioma cell vaccine admixed with interleukin-4 gene transfected fibroblasts in the treatment of patients with malignant gliomas. J Transl Med 2007;5:67.
17. De Vleeschouwer S, Rauws S, Rutkowski S, et al. Postoperative adjuvant dendritic cell-based immunotherapy in patients with relapsed glioblastoma multiforme. Clin Cancer Res 2008; 14:3086-104.
18. Prins RM, Cloughesy TF, Liau LM. Cytomegalovirus immunity after vaccination with autologous glioblastoma lysate. N Engl J Med 2008;359:539-41.
19. Walker DG, Laherty R, Tomlinson FH, Chueh T, Schmidt C. Results of a phase I dendritic cell vaccine trial for malignant astrocytoma, potential interaction with adjuvant chemotherapy. J Clin Neurosci 2008;15:114-21.
20. Wheeler CJ, Black KL, Liu G, et al. Vaccination elicits correlated immune and clinical responses in glioblastoma multiforme patients. Cancer Res 2008;68:5955-64.
21. Sampson JH, Archer GE, Mitchell DA, et al. An epidermal growth factor receptor variant III-targeted vaccine is safe and immunogenic in patients with glioblastoma multiforme. Mol Cancer Ther 2009;8:2773-9.
22. Ardon H, Van Gool S, Lopes IS, et al. Integration of autologous dendritic cell-based immunotherapy in the primary treatment for patients with newly diagnosed glioblastoma multiforme: a pilot study. J Neurooncol 2010;99:261-72.
23. Ardon H, De Vleeschouwer S, Van Calenbergh F, et al. Adjuvant dendritic cell-based tumour vaccination for children with malignant brain tumours. Pediatr Blood Cancer 2010;54:519-25.
24. Chang CN, Huang YC, Yang DM, et al. A phase I/II clinical trial investigating the adverse and therapeutic effects of a postoperative autologous dendritic cell tumor vaccine in patients with malignant glioma. J Clin Neurosci 2011;18:1048-54.
25. Fadul CE, Fisher JL, Hampton TH, et al. Immune response in patients with newly diagnosed glioblastoma multiforme treated with intranodal autologous tumor lysate-dendritic cell vaccination after radiation chemotherapy. J Immunother 2011;34:382-9.
26. Okada H, Kalinski P, Ueda R, et al. Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with {alpha}-type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. J Clin Oncol 2011;29:330-6.
27. Prins RM, Soto H, Konkankit V, et al. Gene expression profile correlates with T-cell infiltration and relative survival in glioblastoma patients vaccinated with dendritic cell immunotherapy. Clin Cancer Res 2011;17:1603-15.
28. Akiyama Y, Oshita C, Kume A, et al. alpha-type-1 polarized dendritic cell-based vaccination in recurrent high-grade glioma: a phase I clinical trial. BMC Cancer 2012;12:623.
29. Ardon H, Van Gool SW, Verschuere T, et al. Integration of autologous dendritic cell-based immunotherapy in the standard of care treatment for patients with newly diagnosed glioblastoma: results of the HGG-2006 phase I/II trial. Cancer Immunol Immunother 2012;61:2039- 44.
30. Cho DY, Yang WK, Lee HC, et al. Adjuvant immunotherapy with whole-cell lysate dendritic cells vaccine for glioblastoma multiforme: a phase II clinical trial. World Neurosurg 2012;77:736-44.
31. De Vleeschouwer, Ardon H, Van CP, et al. Stratification according to HGG-IMMUNO RPA model predicts outcome in a large group of patients with relapsed malignant glioma treated by adjuvant postoperative dendritic cell vaccination. Cancer Immunol Immunother 2012;61:2105-12.
32. Ehlers I, De Vleeschouwer S, Rauwels P, Van Gool SW. Resection and immunotherapy for recurrent grade III glioma. ISRN Immunology 2012;2012:1-6.
33. Fong B, Jin R, Wang X, et al. Monitoring of regulatory T cell frequencies and expression of CTLA-4 on T cells, before and after DC vaccination, can predict survival in GBM patients. PLoS ONE 2012;7:e32614.
34. Iwami K, Shimato S, Ohno M, et al. Peptide-pulsed dendritic cell vaccination targeting interleukin-13 receptor alpha2 chain in recurrent malignant glioma patients with HLA-A*24/A*02 allele. Cytotherapy 2012.
35. Jie X, Hua L, Jiang W, Feng F, Feng G, Hua Z. Clinical application of a dendritic cell vaccine raised against heat-shocked glioblastoma. Cell Biochem Biophys 2012;62:91-8.
36. Qin K, Tian G, Li P, et al. Anti-glioma response of autologous T cells stimulated by autologous dendritic cells electrofused with CD133(+) or CD133(-) glioma cells. J Neuroimmunol 2012;242:9-15.
37. Sampson JH, Schmittling RJ, Archer GE, et al. A Pilot Study of IL2Ralpha Blockade during Lymphocytic Depletion Regulatory T-cells and Correlates with Enhanced Immunity in Patients with Glioblastoma. PLoS ONE 2012;7:e31046.
38. Valle RD, de Cerio AL, Inoges S, et al. Dendritic cell vaccination in glioblastoma after fluorescence-guided resection. World J Clin Oncol 2012;3:142-9.
39. Lasky JL, III, Panosyan EH, Plant A, et al. Autologous Tumor Lysate-pulsed Dendritic Cell Immunotherapy for Pediatric Patients with Newly Diagnosed or Recurrent High-grade Gliomas. Anticancer Res 2013;33:2047-56.
40. Pellegatta S, Eoli M, Frigerio S, et al. The natural killer cell response and tumor debulking are associated with prolonged survival in recurrent glioblastoma patients receiving dendritic cells loaded with autologous tumor lysates. Oncoimmunology 2013;2:e23401.
41. Phuphanich S, Wheeler CJ, Rudnick JD, et al. Phase I trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma. Cancer Immunol Immunother 2013;62:125-35.
42. Prins RM, Wang X, Soto H, et al. Comparison of glioma-associated antigen peptide-loaded versus autologous tumor lysate-loaded dendritic cell vaccination in malignant glioma patients. J Immunother 2013;36:152-7.
43. Vik-Mo EO, Nyakas M, Mikkelsen BV, et al. Therapeutic vaccination against autologous cancer stem cells with mRNA-transfected dendritic cells in patients with glioblastoma. Cancer Immunol Immunother 2013.
44. Eyrich M, Schreiber SC, Rachor J, et al. Development and validation of a fully GMP-compliant production process of autologous, tumour-lysate-pulsed dendritic cells. Cytotherapy 2014;16:949-64.
45. Ishikawa E, Muroi Y, Yamamoto T, et al. Phase I/IIa trial of fractionated radiotherapy, temozolomide, and autologous formalin-fixed tumor vaccine for newly diagnosed glioblastoma. J Neurosurg 2014;121:543-53.
46. Hunn MK, Bauer E, Wood CE, et al. Dendritic cell vaccination combined with temozolomide retreatment: results of a phase I trial in patients with recurrent glioblastoma multiforme. J Neurooncol 2015;121:319-29.
47. Mitchell DA, Batich KA, Gunn MD, et al. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. Nature 2015;519:366-9.
48. Muller K, Henze G, Pietschmann S, et al. Re-irradiation or re-operation followed by dendritic cell vaccination? Comparison of two different salvage strategies for relapsed high-grade gliomas by means of a new prognostic model. J Neurooncol 2015;124:325-32.
49. Sakai K, Shimodaira S, Maejima S, et al. Dendritic cell-based immunotherapy targeting Wilms' tumor 1 in patients with recurrent malignant glioma. J Neurosurg 2015;123:989-97.
50. Van Gool SW. Brain tumor immunotherapy: what have we learned so far? Front Oncol 2015;5:68. doi: 10.3389/fonc.2015.00068.
51. Akasaki Y, Kikuchi T, Homma S, et al. Phase I/II trial of combination of temozolomide chemotherapy and immunotherapy with fusions of dendritic and glioma cells in patients with glioblastoma. Cancer Immunol Immunother 2016;65:1499-509.
52. Pollack IF, Jakacki RI, Butterfield LH, et al. Antigen-specific immunoreactivity and clinical outcome following vaccination with glioma-associated antigen peptides in children with recurrent high-grade gliomas: results of a pilot study. J Neurooncol 2016; 130:517-27.
53. Inoges S, Tejada S, de Cerio AL, et al. A phase II trial of autologous dendritic cell vaccination and radiochemotherapy following fluorescence-guided surgery in newly diagnosed glioblastoma patients. J Transl Med 2017; 15:104.
54. Sakai K, Shimodaira S, Maejima S, et al. Clinical effect and immunological response in patients with advanced malignant glioma treated with WT1-pulsed dendritic cell-based immunotherapy: a report of two cases. Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 2017;9:24-9.
55. Benitez-Ribas D, Cabezon R, Florez-Grau G, et al. Immune Response Generated With the Administration of Autologous Dendritic Cells Pulsed With an Allogeneic Tumoral Cell-Lines Lysate in Patients With Newly Diagnosed Diffuse Intrinsic Pontine Glioma. Front Oncol 2018;8:127.
56. Buchroithner J, Erhart F, Pichler J, et al. Audiencal Immunotherapy Based on Dendritic Cells Has No Effect on Overall and Progression-Free Survival in Newly Diagnosed Glioblastoma: A Phase II Randomized Trial. Cancers (Basel) 2018;10.
57. Jan CI, Tsai WC, Harn HJ, et al. Predictors of Response to Autologous Dendritic Cell Therapy in Glioblastoma Multiforme. Front Immunol 2018;9:727.
58. Erhart F, Buchroithner J, Reitermaier R, et al. Immunological analysis of phase II glioblastoma dendritic cell vaccine (Audencel) trial: immune system characteristics influence outcome and Audencel up-regulates Th1-related immune variables. Acta Neuropathol Commun 2018;6:135.
59. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med 2018;16:142.
60. Pellegatta S, Eoli M, Cuccarini V, et al. Survival gain in glioblastoma patients treated with dendritic cell immunotherapy is associated with increased NK but not CD8(+) T cell activation in the presence of adjuvant temozolomide. Oncoimmunology 2018;7:e1412901.
61. Van Gool SW, Makalowski J, Feyn O, et al. The induction of immunogenic cell death (ICD) during maintenance chemotherapy and subsequent multimodal immunotherapy for glioblastoma (GBM). Austin Oncol Case Rep 2018;3:1010.
62. Yao Y, Luo F, Tang C, et al. Molecular subgroups and B7-H4 expression levels predict responses to dendritic cell vaccines in glioblastoma: an exploratory randomized phase II clinical trial. Cancer Immunol Immunother 2018.
63. Johanns TM, Miller CA, Liu CJ, et al. Detection of neoantigen-specific T cells following a personalized vaccine in a patient with glioblastoma. Oncoimmunology 2019;8:e1569110
64. Rudnick JD, et al. A phase I trial of surgical resection with global water placement followed by vaccination with dendritic cells pulsed with tumor lysate for patients with malignant glioma. J Clin Neurosci 2020;74:187-193
65. Wang QT, et al. Tumor-associated antigen-based personalized dendritic cell vaccine in solid tumor patients. Canc Immunol Immunother 2020;69:1375-1387
66. Van Gool SW, Makalowski J, Bonner ER, et al. Addition of multimodal immunotherapy to combination treatment strategies for children with DIPG: a single institution experience. Medicines 2020;7:29
67. Van Gool SW, Makalowski J, Fiore S, et al. Randomized controlled immunotherapy clinical trials for GBM: challenges. Cancers 2021;13:32

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Efficacy and safety of dendritic cell vaccines for patients with glioblastoma: A meta-analysis of randomized controlled trials

Li Lv[1], Jiangchao Huang[1], Haipeng Xi, Xiangyang Zhou*

Department of Neurosurgery, First Affiliated Hospital, University of South China, Hengyang 421001, Hunan Providence, China

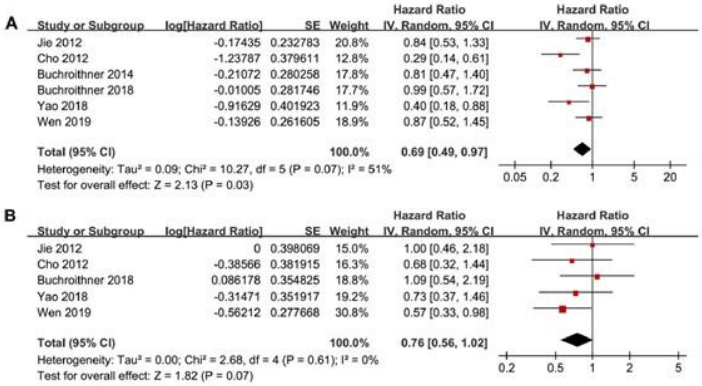

Fig. 2. Forest plots for the meta-analyses comparing the efficacy outcomes between DC-based vaccination and control for glioblastoma; A, overall survival; and B, progression-free survival;

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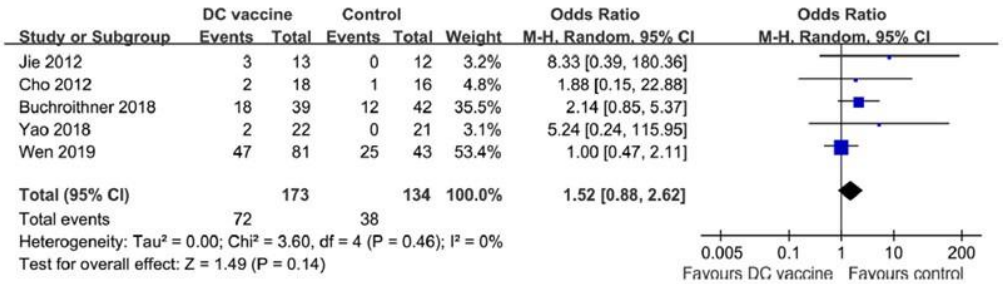


Fig. 3. Forest plots for the meta-analyses comparing the overall incidence of adverse events in patients with glioblastoma allocated to DC-based vaccination and control groups;

Oxford centre for evidence

Level	Therapy/prevention, aetiology/harm	Prognosis
1a	SR (with homogeneity*) of RCTs	SR (with of incepti ies; CDR different
1b	Individual RCT (with narrow Confidence Interval‡)	Individua hort stud follow-up ted in a si
1c	All or none§	All or nor
2a	SR (with homogeneity*) of cohort studies	SR (with of either cohort stu ted contro RCTs
2b	Individual cohort study (including low quality RCT; e.g., < 80% follow-up)	Retrospec study or f treated co als in an R of CDR† split-samp
2c	"Outcomes" Research; Ecological studies	"Outcom
3a	SR (with homoge- neity*) of case-control studies	
3b	Individual Case-Control Study	

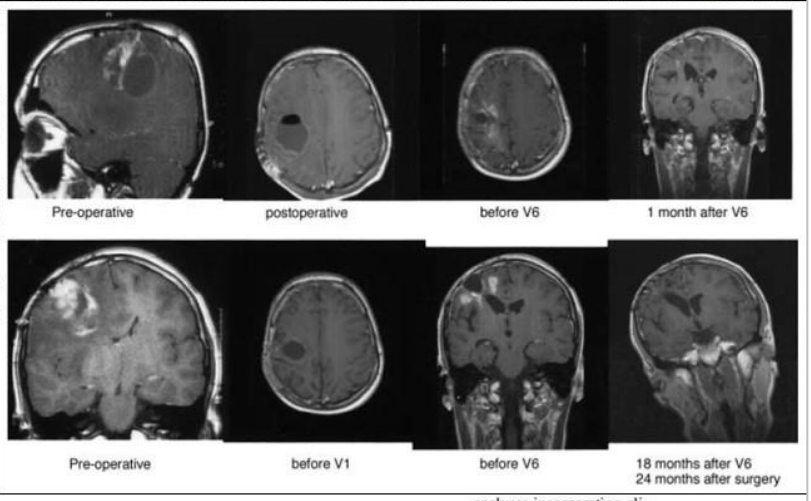
analyses incorporating clinically sensible variations.

J Neurosurg (Pediatrics 5) 100:492–497, 2004

Transient local response and persistent tumor control in a child with recurrent malignant glioma: treatment with combination therapy including dendritic cell therapy

Case report

STEVEN DE VLEESCHOUWER, M.D., FRANK VAN CALENBERGH, M.D., PHILIPPE DEMAEREL, M.D., PH.D., PATRICK FLAMEN, M.D., PH.D., STEFAN RUTKOWSKI, M.D., ECKHART KAEMPGEN, M.D., PH.D., JOHANNES E. WOLFF, M.D., PH.D., CHRISTIAN PLETS, M.D., PH.D., RAF SCIOT, M.D., PH.D., AND STEFAAN W. VAN GOOL, M.D., PH.D.



IOZK | NEW PERSPECTIVES IN CANCER THERAPY

frontiers in Oncology

REVIEW
published: 17 June 2015
doi: 10.3389/fonc.2015.00098

Brain tumor immunotherapy: what have we learned so far?

Stefaan Willy Van Gool *

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HGG-2006

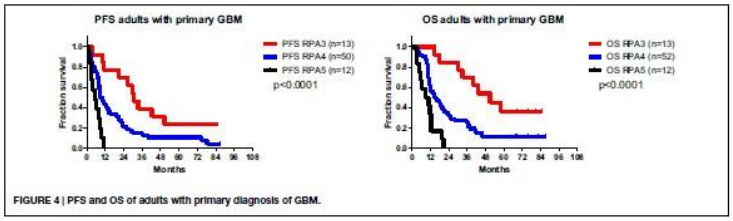

FIGURE 4 | PFS and OS of adults with primary diagnosis of GBM.

HGG-2010
RCT

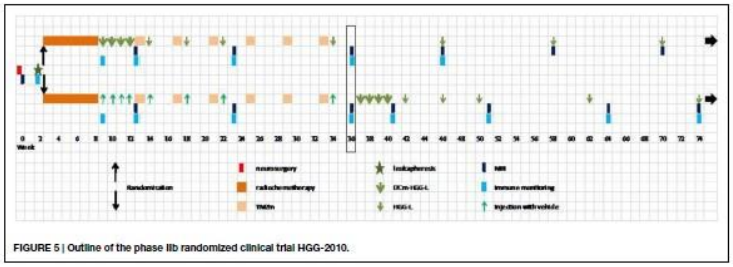

FIGURE 5 | Outline of the phase IIb randomized clinical trial HGG-2010.

Table 1. Risk factors for stratification in randomization or for in/exclusion criteria.

1. Recursive Partitioning Analysis (RPA) clinical classification
   - Grading
   - Extent of resection
   - Age
   - Karnofsky performance index
   - Mental status
   - Dose of radiotherapy
2. Molecular biology of tumor
   - Tumor mutational burden
   - Epigenetic sub-typing
   - Molecular machinery of tumor cell clones
   - Metabolic features of tumor
3. Load of glioma cancer stem cells in connection to periventricular zones of the brain
4. Tumor–host immune reaction
   - Tumor antigen expression
   - Check point expression
   - Inflammatory response, M1/M2 balance, Tumor-associated macrophages, myeloid-derived suppressor cells, microglia reactivity
   - T-cell infiltration
   - Vascularization and oxidative stress
5. Systemic immune compartment
   - Cell numbers under standard of care treatment
   - Th1/Th2 balance
   - Presence of Treg
   - Presence of MDSC
   - Level of natural killer cell reactivity
6. Systemic treatments outside standard of care
   - Steroids
   - Anti-angiogenic drugs
   - Complementary medicines

Van Gool, Cancers 2021

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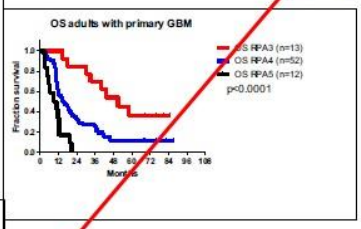
mmunotherapy: what
ned so far?

y, KU Leuven, Leuven, Belgium

Stratifications
Ethical issues
GLP/GTP/GMP/GCP
Costs



Ardon, 2010
Ardon, 2012

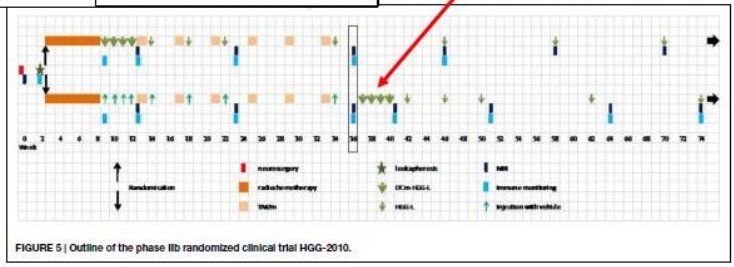


FIGURE 5 | Outline of the phase IIb randomized clinical trial HGG-2010.

HGG-2010
RCT

Antonopoulos, 2019
Dejaegher, 2021

ANTICANCER RESEARCH *39*: 2043-2051 (2019)
doi:10.21873/anticanres.13315

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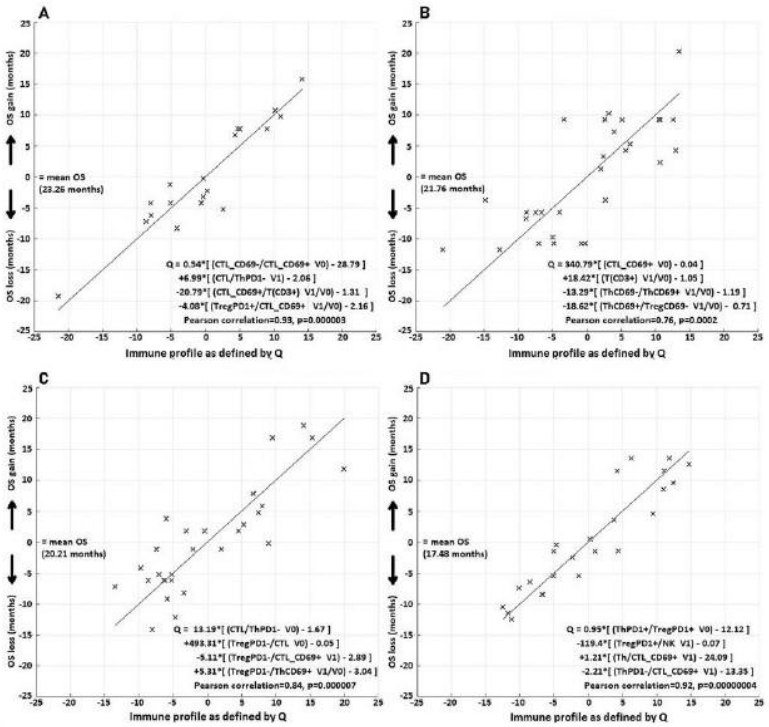
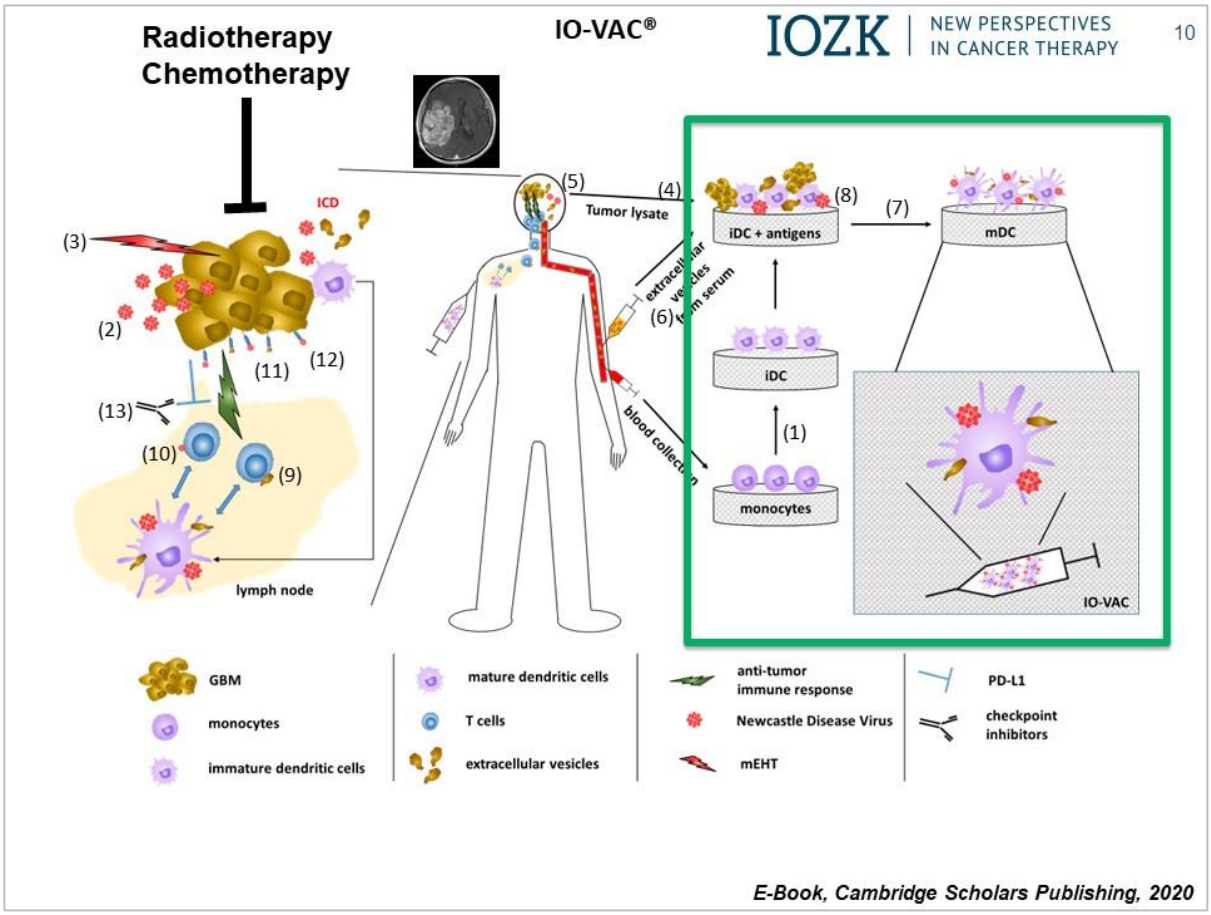


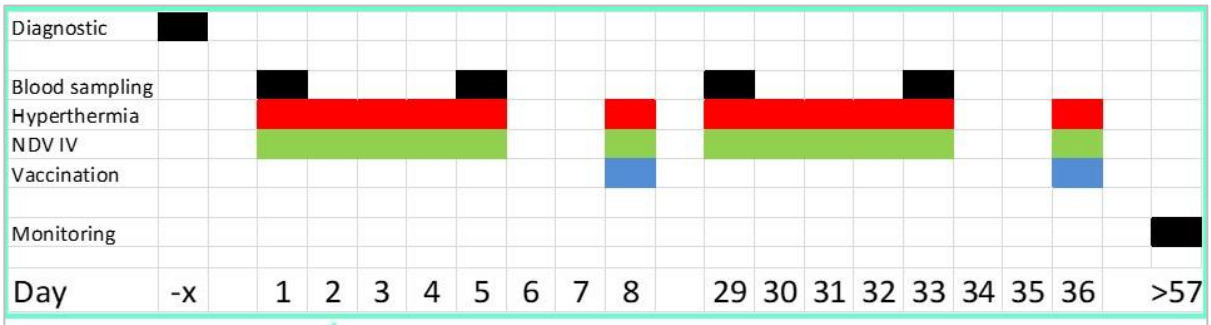
Figure 2. *Canonical correlation analysis of immune profiles versus overall survival (OS). The immune profile is composed of the different FACS-derived quantities (features). Diagrams for four subgroups are shown. A: Vaccination during temozolomide maintenance chemotherapy (TMZm), no residual tumor volume after resection; B: vaccination after TMZm, no residual tumor volume after resection; C: vaccination during TMZm, non-zero residual tumor volume after resection; D: vaccination after TMZm, non-zero residual tumor volume after resection. Each diagram depicts the strong correlation between Q (x-axis), where Q is the sum of quantities of the form: coefficient × [feature − mean of feature in the specific subgroup], and OS (y-axis) expressed as the quantity OS being the individual OS in months minus the mean OS, i.e. mean OS for the specific subgroup.*

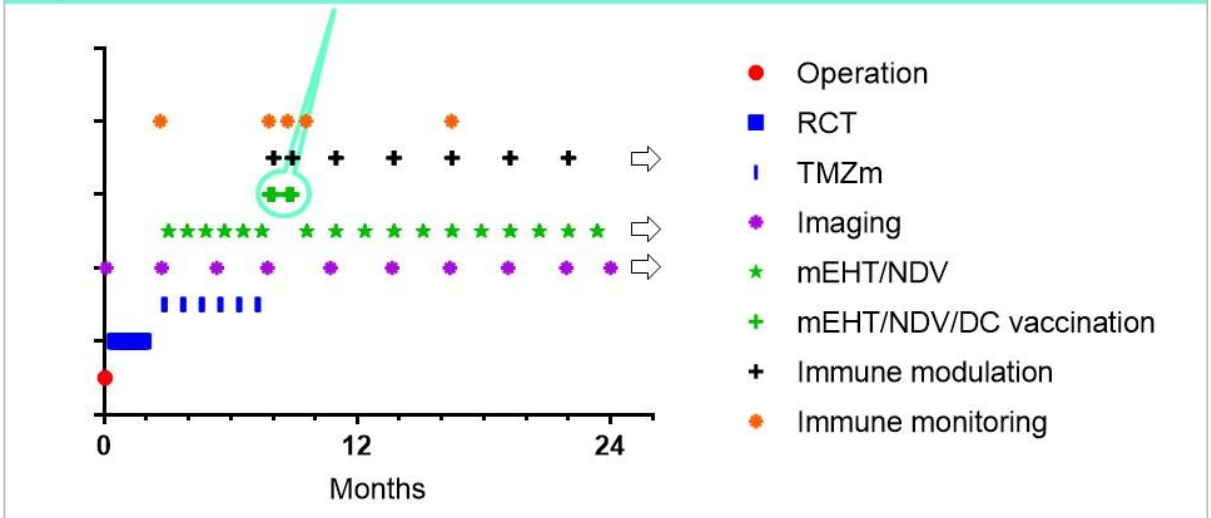
Table I. *Overall survival (OS) data of the total study population and subgroups residual tumor volume (RTV).*

Patient group	No. of patients	Median OS (months)	2-Year OS rate (%)	95%CI
Total group	101	19	33.66	24.66-42.88
Early vaccination, RTV=0	19	22	40.2	18.4-61.2
Late vaccination, RTV=0	29	23	44.8	26.5-61.5
Early vaccination, RTV>0	28	19	25	11-41.7
Late vaccination, RTV>0	25	16	28	12.4-46



E-Book, Cambridge Scholars Publishing, 2020





Van Gool SW, et al. AOCR 2018

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Patient selection

Van Gool, Cancers 2021

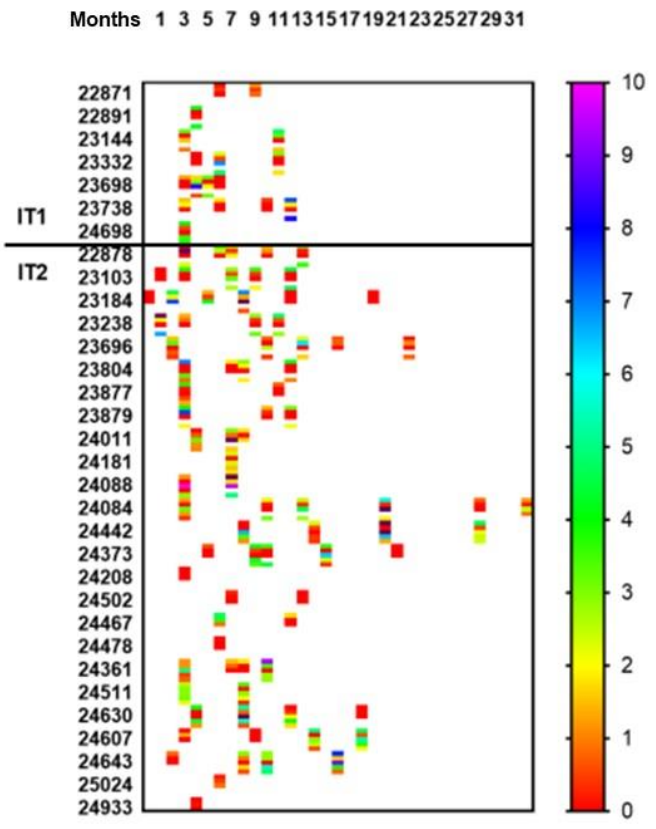
- Database fixed at 08/06/2021
- 5576 records in Database
- 742 records treated 27/05/2015/2015 till 08/06/2021
- 308 neuro-oncology records treated 27/05/2015/2015 till 08/06/2021
- 194 GBM treated 27/05/2015/2015 till 08/06/2021
- 97 GBM treated in first event 27/05/2015/2015 till 08/06/2021
- Further exclusion
  - <18 years; >75 years
  - LGG in history, IDH1 mutation
  - H3K27M mutation (DMG)
  - GBM as second malignancy post-radiotherapy

- 74 adults with primary GBM in first line treatment
- 66 GBM records IT start 1&2
- **32 GBM records IT start 1&2 MGMT promoter documented unmethylated**
- 1 patient LFU

12

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY



ERBB2
C-kit
Telomerase
MGMT
PDL1

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Are fixed treatment protocols appropriate for the treatment of highly dynamic cancers in permanently changing biological contexts ?

Stratifications
Ethical issues
GLP/GTP/GMP/GCP
Costs
Tumor + host dynamics

→

Repetitive liquid biopsy

Maintenance ICD therapies: actual antigens
Repeat active specific immunotherapies
Actualized modulatory immunotherapies

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

IT1: Local therapy -> immunotherapy: **n = 7**
IT2: Surgery -> radiochemotherapy -> TMZm+ICD -> immunotherapy: **n = 25**

	Group-1			Group-2		
Clinical data						
	P25	**Median**	**P75**	**P25**	**Median**	**P75**
Age	36	49	69	41.5	46	57.5
KPI	50	70	95	70	90	100
	R0	**R1**	**ND**	**R0**	**R1**	**ND**
Surgery	1	4	2	10	8	7
Laboratory data						
	L	**N**	**H**	**L**	**N**	**H**
Hemoglobin		7		3	21	1
White Blood cells	1	5	1	2	19	4
Platelets	4	3		5	20	
T cells	2	4		13	12	
B cells	6			22	2	1
NK cells	3	3		15	10	
NK cell function	5		1	13	8	2
CD4 IFNg	1	4		1	19	2
CD4 IL4	1	5		2	13	8
	CCC-	**CCC+PDL1-**	**CCC+PDL1+**	**CCC-**	**CCC+PDL1-**	**CCC+PDL1+**
CCC	2	2	1	9	9	5
Treatment data						
	P25	**Median**	**P75**	**P25**	**Median**	**P75**
IO-Vac®	1	2	2	1	2	2
Total DCs	11600000	15400000	38300000	7200000	24000000	36450000
Total NDV injections	6	15	24	24	42	47
Total mEHT sessions	4	11	24	17	39	46

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

IT1: Local therapy -> immunotherapy: **n = 7**

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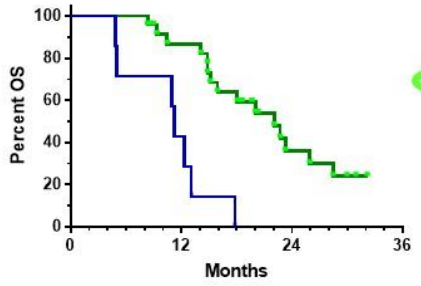
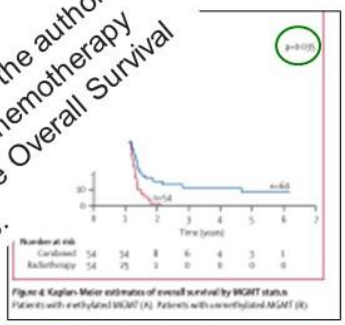




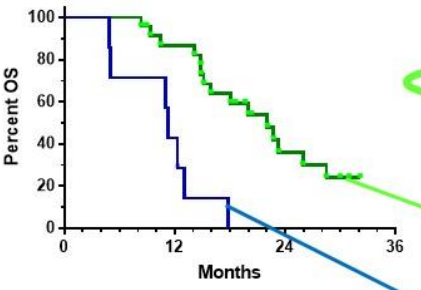
Genes & Immunity Review 26.10.2021
This is a ***really interesting clinical study*** *from Van Gool et al. where the authors investigated the synergyism between the widely utilized anti-GBM chemotherapy like TMZ and individualized multimodal immunotherapy to improve Overall Survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients.*

mOS months	OS	2y OS
S + RT (Stupp, 2009)	*1.8*	*1.8% (0.1-8.6)*
S ± RT + **IO-Vac®**	**11.25**	**0%**
S + RCT + TM	*12.6*	*14.8% (7-2-25)*
S + RCT **+ ICDm**	**22.07**	**36% (15.7-56.8)**

SYNER Z and individualized multimodal immunotherapy to improve wild type MGMT promoter-unmethylated GBM patients

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY



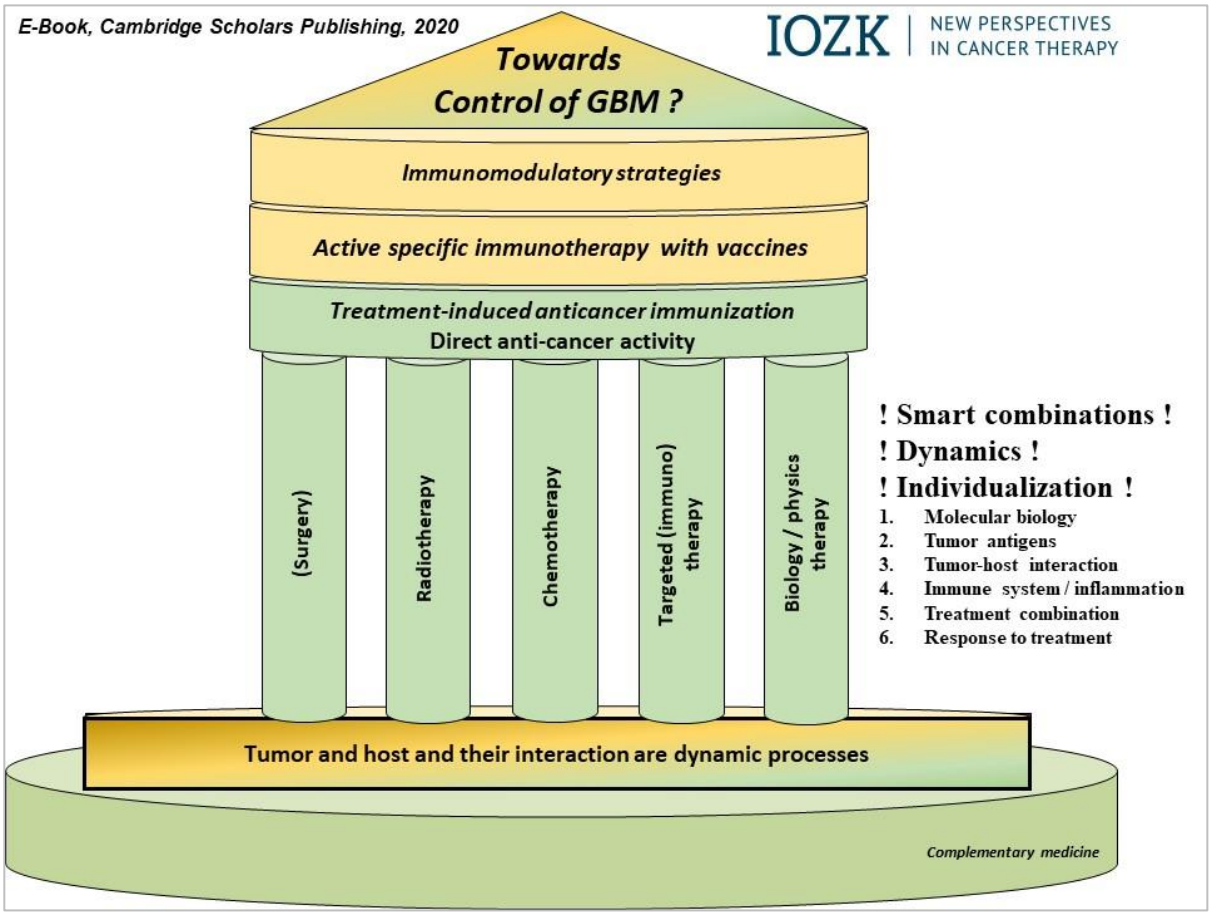
EQ-5D-5L (3125 situations)
* *MO*: Mobility: 1-5
* *SC*: Self-Care: 1-5
* *UA*: Usual Activities: 1-5
* *PD*: Pain/Discomfort: 1-5
* *AD*: Anxiety/Depression: 1-5

VAS: 0-100
KPI: 0-100

Euro	Intake	ICD (**)	DC	Other (*)	Other% (***)	Total	Months	Cost/month
				IT2 (=17 deceased patients)				
Median	3500,00	5850,00	17600,00	36093,00	55,81	69100,00	13,06	**4725,00**
Min	3000,00	780,00	0,00	11161,00	37,83	17480,00	3,00	2150,00
Max	3500,00	14040,00	42600,00	79872,00	76,64	122876,00	24,00	17314,00
				IT1 (n=7)				
Median	3000,00	2145,00	17600,00	14242,00	39,98	36213,00	5,86	**7124,00**
Min	3000,00	780,00	15400,00	6015,00	23,06	26085,00	1	4024,00
Max	3500,00	5265,00	30100,00	32371,00	53,74	70736,00	10	28626,00

SYNERGY between TMZ and individualized multimodal immunotherapy to improve OS of IDH1 wild type MGMT promoter-unmethylated GBM patients

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*



IOZK | NEW PERSPECTIVES IN CANCER THERAPY

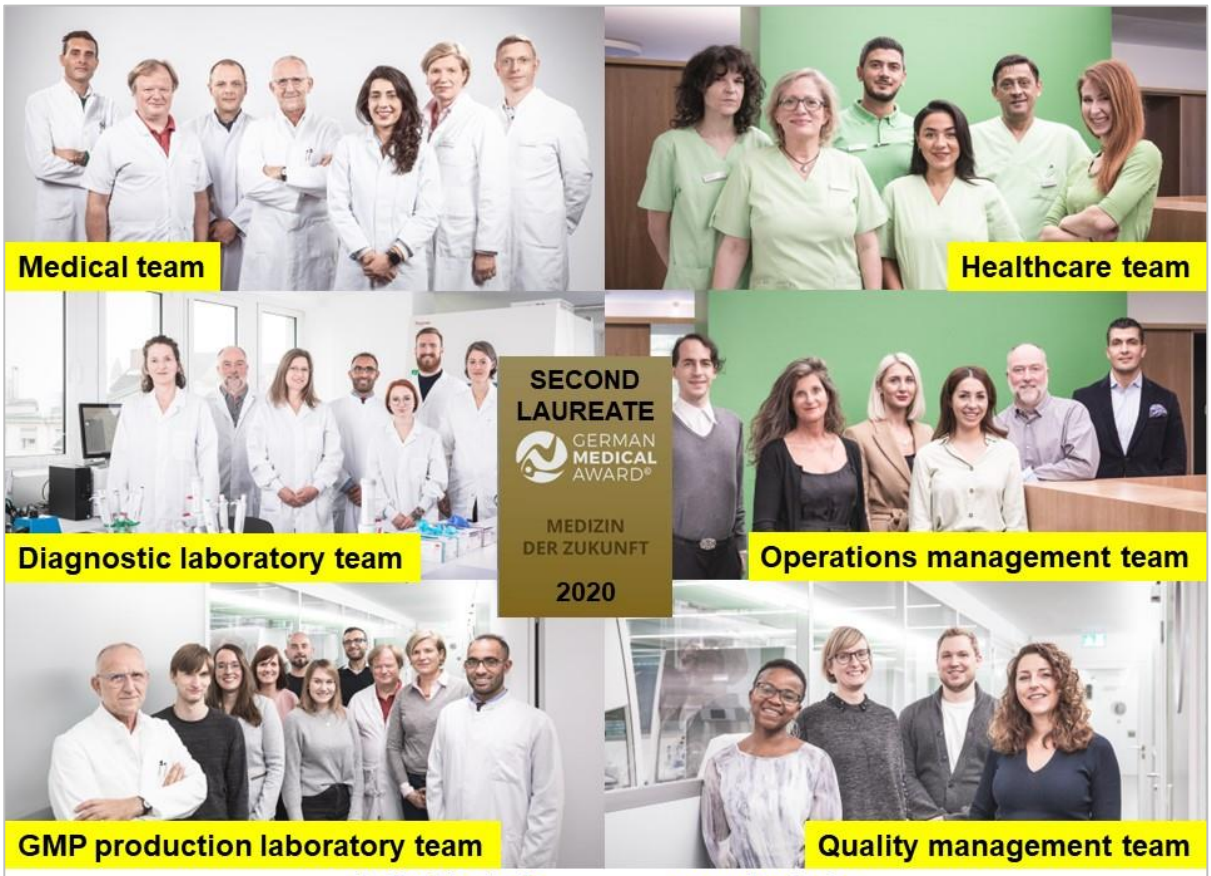
Conclusion

- **Individualized multimodal immunotherapy**
  can/should be integrated within the **Standard of Care first line treatment for patients with GBM**
- **Old-fashioned RCTs** with fixed treatment protocols are not useful to study complex treatments in **highly dynamic biological processes**
- Focus on **prolongation of life with good quality of life**: EQ-5D-5L
- **Current optimal scenario**
  1. **Surgery**
  2. **Radiochemotherapy**, ± **ICD therapy**
  3. Immune diagnostics
  4. **Maintenance chemotherapy** + **ICD therapy**
  5. 2x Active specific immunotherapy **IO-Vac®** ± Modulatory immunotherapy
  6. Monitoring + ICDm1 therapy ± Modulatory immunotherapy
  7. **Maintenance ICD therapy ± Modulatory immunotherapy** / Monitoring
- **In „Individueller Heilversuch“**

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Collaboration is opportunity

- **Current optimal scenario**
  1. **Surgery**
  2. **Radiochemotherapy**, ± **ICD therapy**
  3. Immune diagnostics
  4. **Maintenance chemotherapy** + **ICD therapy**
  5. 2x Active specific immunotherapy **IO-Vac®** ± Modulatory immunotherapy
  6. Monitoring + ICDm1 therapy ± Modulatory immunotherapy
  7. **Maintenance ICD therapy ± Modulatory immunotherapy** / Monitoring
- **In „Individueller Heilversuch“**
- **Collaboration**
  - **Sharing data under „IOZK patient“**
  - **Ownership of own data and anonymized data from the group**
  - **Co-authorship in common publications**



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Tumors of the hepato-pancreato-biliary system: can we tame the beast?

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Cite this article as:
Szász, A.M. (2022): Tumors of the hepato-pancreato-biliary system: can we tame the beast?

Oncothermia Journal 32, September 2022: 62 – 74.
www.oncotherm.com/sites/oncotherm/files/2022-09/SzaszM_ICHS_Tumors_of_hepato-pancreato-biliary.pdf

Tumors of the hepato-pancreato-biliary system: can we tame the beast?

Szász, A. Marcell, MD, PhD, Habil.
Semmelweis University, Department of Internal Medicine and Oncology
Budapest

Questions

Adjuvant hyperthermia is beneficial in hepatopancreatobiliary cancers?

What about treatment response, survival, and laboratory and quality of life data?

In this overview, the clinical data on hyperthermia in hepatopancreatobiliary tumors is summarized.

a comprehensive guide to

Yellow Stripey Things

Carpenter Bee
-acts like it's hot shit but can't actually hurt you
-has no concept of what glass is
-lives in your fence
-flies aggressively to try and scare you away

Honeybee
-is the bee that needs help the most
-excellent pollenator
-very friendly
-can only sting once

Bumblebee
-also pollenates stuff very well
-so fat it shouldn't be able to fly
-will let you pet it without getting agitated
-actually a flying panda

Hoverfly
-wears yellow stripey uniform to scare you
-actually can't do anything to you
-hangs out in fields
-follows you if it likes you

Paper Wasp
-looks scary, but will only attack if provoked
-sting hurts like hell
-will chase you if you swat at it
-has no concept of personal space

Yellow Jacket
-wants your food and will fight you for it
-never leaves you alone
-will sting you just for the hell of it
-is just an asshole

Cicada Killer
-looks like Satan's nightmares
-exclusively eats cicadas
-can sting you, but usually won't
-still pretty terrifying

Dirt Dauber
-almost never stings anything except spiders
-builds nest in the ground
-hoards spiders in said nest
-coolest looking of the wasps

In fact... Hepatopancreatobiliary tumors

PANCREAS HEPATOCELLULAR CHOLANGIOCELLULAR

honey bee *bumble bee* *wasp*

https://www.almanac.com/wasps-bees-and-hornets-whats-difference

Hepatopancreatobiliary (HPB) cancers

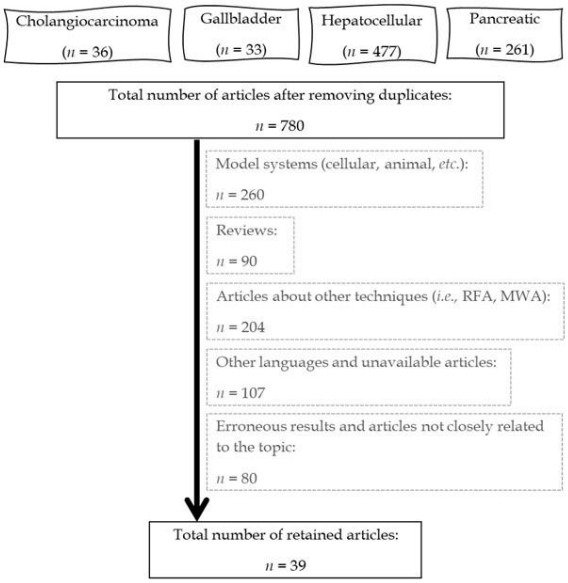
- Fatal diseases that can be characterized by **very low 5-year survival rates**[1-3].
- In 2018, over **1.5 million new cases** and approximately **1.4 million deaths** from hepatocellular (HCC), biliary (BC) including gallbladder and cholangiocellular (CCC), and pancreatic cancers (PC) were reported[4].
- Diagnosis at a **more advanced stage** is characteristic to all four tumor types[1-3], which is usually accompanied by **other comorbidities** like a cirrhotic state of the liver, which further worsens patient life expectancy [1].
- In the last decades**, several new techniques** and possible multimodal therapies have emerged that support conventional surgical resection and facilitate chemoradiotherapy, including but not limited to various thermal ablative methods[5] including radiofrequency[6] and microwave ablation[7], laser-induced thermotherapy[8], hyperthermic intraperitoneal chemotherapy[9], percutaneous ethanol injection[10], transcatheter arterial chemoembolization[11], high-intensity focused ultrasound[12], and various types of hyperthermia[13].
- The available **literature** on the clinical applications of hyperthermia in hepatopancreatobiliary cancers will be discussed focusing on survival and safety data.

Methods

- A literature search was conducted in **PubMed/MEDLINE** using the strings "cholangiocarcinoma hyperthermia", "gallbladder cancer hyperthermia", "hepatocellular hyperthermia", and "pancreatic cancer hyperthermia", for articles published **from January 1, 1964 to January 31, 2021**. After removing duplicates, a total of 780 potential articles were found, from which 39 full-text articles were selected. A secondary search in **ClinicalTrials.gov** was conducted, and an additional three finished and four currently running clinical trials were identified. Five additional studies were included from another search in meta-analysis and review citations, raising the **total number of 47 publications** included in this review.
- Figures were drawn with R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria, 2021) and the R package forestplot (version 1.10.1, Max Gordon and Thomas Lumley, 2020). Data were obtained from eligible articles, and a simple difference in overall survival and disease control rate (the sum of complete or partial response to treatment and stable disease) was calculated from the results of the cohorts with and without hyperthermia.

Flow diagram of the selection of PubMed/Medline articles.

MWA: Microwave ablation;
RFA: Radiofrequency ablation.



Hyperthermia in pancreatic cancer (PC)

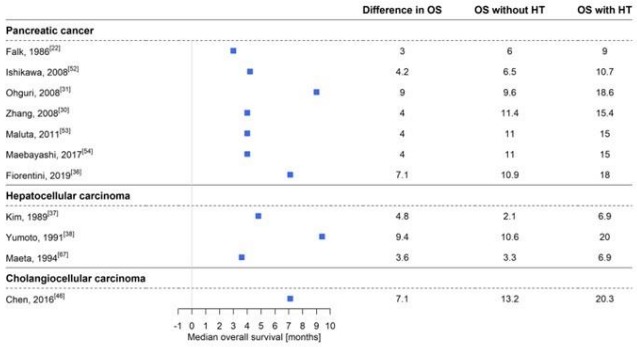
- **Current treatment options** for PC are surgical resection with postoperative chemoradiotherapy, and systemic chemotherapy for borderline resectable and locally advanced or metastatic PCs[3].
- Historically **5-fluorouracil** was the most used chemotherapy agent in advanced and metastatic PCs, but was replaced by **gemcitabine and FOLFIRINOX** (folinic acid + 5-fluorouracil + irinotecan + oxaliplatin) starting in the mid-1990s[48,49].
- **Hyperthermia has been introduced as an auxiliary treatment for advanced and metastatic PCs.**
- **Whole-body hyperthermia** was shown to improve the effect of melphalan on blood cell counts in refractory cancers including PC[26], but no such effect was observed if carboplatin was administered alone[25].
- A treatment regimen of **monthly cisplatin + gemcitabine with whole-body hyperthermia** combined with continuous **low-dose interferon-α** had somewhat improved survival compared with standard chemoradiotherapy in metastatic PC, and a higher partial response rate to thermo-chemotherapy[27].
- In another study, advanced PC patients, who had achieved **partial remission**, had longer median survival than those who had not responded to the treatment (11.4 mo *vs* 15.8 mo)[28].
- A **clinical study (NCT04467593) is currently investigating the effects of whole-body hyperthermia** on current chemotherapy with gemcitabine and FOLFIRINOX[50].

PC cont.

- Several studies demonstrated that **thermo-chemotherapy** of locally advanced or metastatic PCs *via* **regional hyperthermia** had a positive effect on patient survival and therapeutic efficacy. During the last three decades, multiple chemo, radio, and other therapies and procedures were combined with regional hyperthermia in PC[22,23,29-36,47,51-59].
- In detail, **thermo-chemotherapy with selective immune stimulation** resulted in longer patient survival[22].
- In other studies[23,51], patients treated with **chemoradiotherapy and complementary hyperthermia** had **better disease control rates** than those without hyperthermia, **doubling the observed responses** to treatment. Furthermore, the partial response rate increased along with increased maximum output power of the hyperthermia device[51].

Differences in median overall survival between cohorts treated with and without hyperthermia.

HT: Hyperthermia;
OS: Overall survival.



PC cont.

- After the introduction of routine clinical use of **gemcitabine and FOLFIRINOX**, several studies investigated the effect of **regional hyperthermia** on those treatments[29,31-35,47,52-57].
- **Gemcitabine** alone had worse overall survival and treatment response than when used with **complementary hyperthermia**[29,47,52], and better progression-free and overall survival have also been reported with the concomitant use of hyperthermia in combination with radiotherapy[31,53,54].
- The previous observation that **increasing the power output** of the hyperthermia device increases treatment response[51] **was not confirmed** in the case of gemcitabine[31]. **Other chemotherapeutic agents** such as cisplatin[33,34] or oxaliplatin[32] had similar results. Patients in the hyperthermia arm had better partial response rates and better survival than those without hyperthermia.
- In addition, the currently running **HEAT (NCT01077427)[60] and HEATPAC (NCT02439593)[61,62] clinical trials** will further broaden our knowledge of the efficacy and safety of hyperthermia combined with gemcitabine in PC.

PC cont.

- A few case reports have been published recently where chemoradiotherapy and hyperthermia were combined with **herbal remedies**. One German[56] and two Italian[57] reports described treating metastatic PC patients with chemoradiotherapy and hyperthermia supplemented with subcutaneous, fever-inducing **mistletoe** (*Viscum album*) extract and other immunomodulating supplements including **curcumin or shiitake** (*Lentinula edodes*) derivatives. All three patients had survived more than 30 mo with unrestricted quality of life; no deaths were reported at the time of publication[56,57].
- As with conventional regional hyperthermia, positive effects of **mEHT** on progression-free and overall survival, and on improved disease control rate have been observed[36,58]. Metastatic tumors, including PC patients with ascites, have shown better response (absorption of ascites) and quality of life when **mEHT with traditional Chinese herbal remedy** therapy was administered, compared with patients on chemotherapy and regular drainage[59]. A possible correlation between the time from diagnosis to the first mEHT treatment and the survival time from first mEHT treatment was proposed[36].

Hyperthermia in HCC

- **Early-stage HCCs** are treated with surgical resection or liver transplantation, radiofrequency or microwave ablation, or embolization methods with or without chemoradiotherapy.
- **Intermediate and advanced-stage HCCs** are generally treated with systemic and combination therapies[1]. Early studies of **hyperthermia in HCC** investigated the combination of hyperthermia with chemoradiotherapy, transarterial embolization, or transcatheter arterial chemoembolization[23,37-41,63-69]. Significantly longer survival, lower serum alpha-fetoprotein levels, and better response to treatment, even in tumors > 7 cm[23], were observed in those reports[23,37-41,63-69].
- According to the results of one study[64], the best results were achieved if the intratumor **temperature reached > 42 °C**, while in another study[39] **tumors located in the left lobe** of the liver were more responsive to combined treatment with hyperthermia. The latter observation may have resulted from a technical aspect of the treatment, as noted by the authors[39]. In addition to the above, investigations of which treatment option benefits the most from hyperthermia in HCC have found that the best survival and response data have been observed in cases of **immunotherapy with hyperthermia**[41].

HCC cont.

- **Combining** transcatheter arterial chemoembolization, radiotherapy and hyperthermia[43,44], conformal radiotherapy with hyperthermia[20], and mEHT with sorafenib[42] or traditional Chinese herbal remedy therapy[59] were shown to **improve the normalization of laboratory results, disease control rate, progression-free and overall survival, and 1-year recurrence and mortality rates**.
- Results of the **CERT[43,44] study** supplement the above with the following:
  - (1) **radiotherapy related gastroduodenal toxicity** (*e.g.*, ulcers, gastroduodenitis, and others) was significantly **lower** in the hyperthermia cohort; and
  - (2) patients with better tolerance for higher power hyperthermia had the same treatment response rate and survival, suggesting that an **increased power output level did not add to treatment efficacy.**

HCC cont.

- It is known from model systems[70-72] that **heating to fever-range temperatures improves the immune response against tumors, while tumoricidal temperatures (> 42 °C) inhibit host competence.**
- Because of the latter observation, **whole body hyperthermia at tumoricidal temperatures is considered to have an unfavorable effect** on the immune system, while regional hyperthermia does not have this effect, as the tumor-surrounding tissue only heats to fever-like temperatures[70-72].
- Investigation of the $CD4^+$ and $CD8^+$ T, and natural killer (NK) cell immunity after the first treatment and after a whole hyperthermia treatment course in HCC[72] revealed that **antitumoral changes occur in those cells and last up to at least 2 mo**:
  - **NK cells are the first to respond to hyperthermia**. Increased NK cell activity has been observed in patients with below normal or normal levels of pretreatment NK activation. Patients with increased pretreatment NK activity had a slight decrease after treatment, but the difference was not statistically significant.
  - $CD4^+$ **T cell activation** was slightly decreased and $CD8^+$ increased, both after the first and after the complete hyperthermia regimen[72].

Hyperthermia in CCC

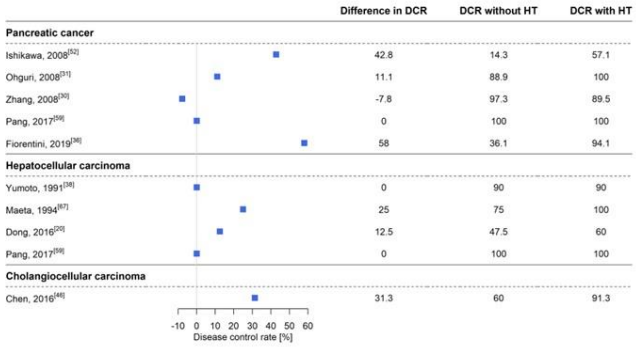
- Of the hepatopancreatobiliary cancers, hyperthermia is the least studied in CCC.
- Conventional **treatment options** of CCC are similar to those of PC and HCC; surgical resection for resectable cases and chemoradiotherapy and systematic combination therapies for advanced and metastatic cases[2].
- Until the mid-2000s no studies had been specifically designed to investigate hyperthermia in CCC.
- The results of studies investigating the effect of hyperthermia on mixed tumor types are available[26,29,41,51,63,64], in which a few biliary cases were also presented.
- **Positive effect of hyperthermia on tumor response rate, tumor markers, and survival have been reported**[26,29,41,51,63,64]; and the **combination of hyperthermia** and transcatheter arterial embolization, chemo- or radiotherapy have been considered as equally good combinations of possible therapies in advanced tumors of the biliary tract[41].

CCC cont.

- **Adjuvant hyperthermia with chemotherapy** has increased the treatment response rate and overall survival of CCC patients[74,75].
- Improvements in **quality of life** (*i.e.* fewer tumor related symptoms) and laboratory results were reported in a detailed case report of a patient with unresectable hilar CCC[75].
- Similarly, extending hepatic arterial infusion chemotherapy with hyperthermia in patients with advanced CCC have resulted in **longer progression-free and overall survival and in better disease control rate**[45,46]. The positive effects of hyperthermia were observed after the first few treatments[46], complete responses have been reported[46], and no increased toxicity after chemotherapy occurred[45].

Differences in the disease control rate between cohorts treated with and without hyperthermia.

DCR: Disease control rate; HT: Hyperthermia.



Core tip

- Adjuvant hyperthermia is beneficial in hepatopancreatobiliary cancers because of its direct and indirect antitumor effects.
- Increased treatment response, prolonged survival, and improved laboratory and quality of life data have been observed in several randomized and observational clinical trials of various hyperthermia methods.
- Regional hyperthermia and mEHT is more advantageous and more accepted among patients than whole-body hyperthermia.
- However, the use of hyperthermia in cancer care is not yet routine.
- A refined or subdivided stage 4 category would be most beneficial to stratify the patients according to tumor load and involved organs, supplemented by serum tumor marker levels.

Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients

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Cite this article as:
Minnaar, C.A. et al. (2022): Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients. Cancers 2022, 14, 656. https://doi.org/10.3390/cancers14030656

Oncothermia Journal 32, September 2022: 75 – 94.
www.oncotherm.com/sites/oncotherm/files/2022-09/Minnaar_Effects_of_mEHT.pdf

Simple Summary:
More than 80% of global cervical cancer cases and deaths occur in Low-to- Middle-Income Countries. Improving the efficacy of treatments without increasing the costs in these regions is therefore imperative. The aim of our Phase III Randomised Controlled Trial was to investigate the effects of the addition of a mild heating technology, modulated electro-hyperthermia,to chemoradiotherapy protocols for the management of locally advanced cervical cancer patients in a resource-constrained setting. We previously reported on the positive outcomes on local disease control, quality of life, and early toxicity. Our recent results showed a significant improvement in two and three year disease free survival, without any significant changes to the toxicity profile, andwith an improvement in quality of life, alongside a cost saving over three years. The effect was mostsignificant in patients with Stage III disease, and a significant systemic effect was observed in patients with distant nodal metastases.

Abstract:
(1) Background: Modulated electro-hyperthermia (mEHT) is a mild to moderate, capacitive- coupled heating technology that uses amplitude modulation to enhance the cell-killing effects of the treatment. We present three year survival results and a cost effectiveness analysis from an ongoing randomised controlled Phase III trial involving 210 participants evaluating chemoradiotherapy (CRT) with/without mEHT, for the management of locally advanced cervical cancer (LACC) in a resource constrained setting (Ethics Approval: M120477/M704133; ClinicalTrials.gov ID: NCT033320690).

(2) Methods: We report hazard ratios (HR); odds ratio (OR), and 95% confidence intervals (CI) for overall survival and disease free survival (DFS) at two and three years in the ongoing study. Late toxicity, quality of life (QoL), and a cost effectiveness analysis (CEA) using a Markov model are also reported.

(3) Results: Disease recurrence at two and three years was significantly reduced bymEHT (HR: 0.67, 95%CI: 0.48–0.93, p = 0.017; and HR: 0.70, 95%CI: 0.51–0.98, p = 0.035; respectively). There were no significant differences in late toxicity between the groups, and QoL was significantlyimproved in the mEHT group. In the CEA, mEHT + CRT dominated the model over CRT alone.

(4) Conclusions: CRT combined with mEHT improves QoL and DFS rates, and lowers treatment costs, without increasing toxicity in LACC patients, even in resource-constrained settings.

Keywords:
modulated electro-hyperthermia; abscopal effect; locally advanced cervical cancer; resource-constrained setting; radiosensitiser

1. Introduction

Around 602,127 new cases of cervical cancer and an estimated 341,831 deaths from cervical cancer were reported globally in 2020. More than 80% of these cases and deaths occurred in Low-to-Middle-Income-Countries (LMICs) [1], creating significant socio-economic stress in these resource-constrained settings [2]. The problem is compounded by poor screening programs [2], limited access to adequate treatments [3], and the high incidence of Human Immunodeficiency Virus (HIV) infections in these regions [4]. While developed countries are estimated to achieve the elimination goal of four cases per 100,000 women- years by 2060, LMICs are expected to only reach this goal towards the end of the century [2]. Improving treatment outcomes, without significantly increasing the costs, is therefore crucial to the management of the disease in these regions. Hyperthermia (HT) is a known radiosensitiser [5], and has proven to be a beneficial adjunct to radiotherapy (RT) and chemoradiotherapy (CRT) for the management for locally advanced cervical cancer (LACC) in developed settings [6]. Classical HT techniques include capacitive and radiative heating technologies, both of which have demonstrated efficacy at improving outcomes in cervical cancer [7–9]. Classical HT uses temperature-dependent dosing calculations such as CEM43 and TRISE [10,11] to optimise the treatment outcomes, although the optimal temperature and timing is still a topic of discussion [12,13].

There is emerging evidence that radiofrequency (RF) electromagnetic fields associated with some HT techniques have additional effects during the treatments [14]. Modulated electro- hyperthermia (mEHT) is a mild- to moderate-heating technology that applies 13.56 MHz RF waves generated by a capacitive coupling set-up between two electrodes. The amplitude of the waves is modulated with a signal equivalent to 1/f noise, where the power density (S(f)), (or power per frequency interval), of the 1/f amplitude-modulated signal is inversely proportional to the modulation signal: S(f)~1/f. The amplitude modulation (AM), and the precise impedance matching (which allows for the cellular selection and the relatively low applied power),

are the main differences between mEHT and classical capacitive HT technologies [15]. Pre-clinical studies have shown that the modulation induces a non-thermal field effect which enhances the cell–killing of the thermal effect by a factor of 3.2 [16]. This appears to make mEHT more effective when adjusted to the same temperature as other heating techniques in pre-clinical studies [17]. It has even been proposed that the AM could be the most important characteristic of mEHT [18]. Pre-clinical studies have shown several immune-related effects of mEHT, which, if applied clinically, could promote the recognition and the targeting of tumours by the immune system [19–22].

This technique proposes a dosing paradigm based on energy deposition and absorption, with thermal effects being an outcome of the treatment, and not the goal of the treatment. The biophysics of the technology are described in detail elsewhere in the literature [23,24]. The lower power output, lower temperatures achieved [25], and non-thermal dosing parameters negate the need for thermal monitoring as safety and dosing parameters during mEHT. This has led to opposing opinions regarding the grouping of mEHT with classical HT techniques.

While there are numerous Phase I/II trials on mEHT, and some small double arm studies [26], there have not been any completed Phase III Randomised Controlled Trials (RCT) on mEHT. We previously reported preliminary results from an ongoing Phase III RCT which is investigating the effects of CRT with or without mEHT for the management of LACC in a resource-constrained setting in South Africa. The primary outcome was two year overall survival (OS), and the secondary outcome was local disease control (LDC) at six months post-treatment. The LDC results, as summarised in Table 1 [27], and a detailed safety and toxicity analysis [28], have been reported previously. The Odds Ratios (OR) for achieving LDC and Local Disease Free Survival (LDFS) at six months post-treatment were 0.39 (95%CI: 0.20–0.77; p = 0.006) and 0.36 (95%CI: 0.19–0.69; p = 0.002), respectively, in favour of the administration of mEHT [27].

Table 1. Summary of the local disease control results at six months post-treatment [27].

210 Randomised Participants	Total		mEHT		Control		Chi Squared
	n	%	*n*	%	*n*	%	
Eligible for analysis	202	96.2%	101	50.0%	101	50.0%	
Alive at six months post-treatment	171	84.7%	88	87.1%	83	82.2%	$p = 0.329$
LDC achieved	60	29.7%	40	45.5%	20	24.1%	$p = 0.003$
LDFS achieved in those who survived six months post-treatment	59	29.2%	39	38.6%	20	19.8%	$p = 0.003$

Abbreviations: LDC: Local Disease Control; LDFS: Local Disease Free Survival; mEHT: Modulated electro-hyperthermia.

The addition of mEHT did not affect the early toxicity profile of the prescribed CRT. In the mEHT Group, 97% of the participants were able to receive 8 out of the 10 prescribed mEHT treatments, with 9.5% of participants in the mEHT group reporting grade 1–2 adi- pose burns, 2% reporting grade 1 surface burns, and 8.6% reporting pain during the mEHT treatments [28]. The average BMI of the participants was 27.8 [15–49]. A multivariate anal- ysis showed that energy dose in kilojoules, HIV status, and Body Mass Index (BMI) were not significant predictors of adverse events. Body Mass Index was also not significantly predictive of LDC. This suggests that mEHT is able to penetrate thicker layers of adipose tissue than conventional capacitive heating technologies, without significant damage to the adipose tissue [28]. The addition of mEHT was also associated with a significantly greater improvement in cognitive function at six weeks post-treatment, a significant reduction in pain and fatigue, and a significant improvement in social and emotional functioning at three months post-treatment [28]. An unexpected observation was the potentiation of the abscopal effect. An analysis of the sub-group of participants with extra-pelvic nodal disease visualised on the pre-treatment 18F-FDG PET/CT scans showed that 24.1% (13 out of 54) of those who were treated with mEHT had complete metabolic resolution of all disease on the follow-up 18F-FDG PET/CT scans, compared to 5.6% (3 out of 54) of the participants who did not receive mEHT (Chi squared: p = 0.013). A multivariate analysis showed that the outcomes were not associated with the administration of cisplatin or with the participants' HIV-status. These results suggested the potentiation of an abscopal effect by mEHT, as the locally applied RT resulted in the resolution of distant disease, when combined with mEHT. These findings are elaborated in the paper by Minnaar et al. [29].

The preliminary results showed a significant short-term benefit with the addition of mEHT to CRT, without a significant increase in toxicity, in our resource-constrained setting. We present the two and three year OS results, and preliminary results from a cost effectiveness analysis (CEA) on the use of mEHT in public and private healthcare settings. Local disease control may be associated with a short-term improvement in

quality of life and with OS; however, long-term DFS results hold more relevance as DFS may be associated with sustained improvements in quality of life and affect the socio-economic impact of the disease. The follow-up results presented in this paper are the first long-term results reported from a Phase III RCT on mEHT and they are an important contribution to the understanding of the long-term clinical impact of mEHT in the management of LACC. The CEA provides valuable insight into the feasibility of incorporating mEHT into clinical practice that can be applied to both developed and resource-constrained settings.

2. Materials and Methods

The trial (ClincialTrials.gov ID: NCT03332069), was approved by the Human Research and Ethics Committee (HREC) on 4 May 2012 (ID: M120477) and registered on the National Clinical Trial Database (ID: 3012) before recruitment began. Due to the significant improvment seen in the mEHT Group early on in the study, the follow-up period was extended from two to five years post treatment on 5 May 2017 (M704133). All patients (or their legal representatives) provided written informed consent before enrolment.

Participants: Inclusion criteria included females with treatment-naïve, histologically confirmed FIGO stage IIB (with invasion of the distal half of the parametrium) to IIIB squamous cell carcinoma of the uterine cervix (staged clinically using a chest X-ray, abdominopelvic ultrasound, and clinical examination); eligible for RT with radical intent; and a creatinine clearance > 60 mL/min (calculated according to the Cockcroft-Gault equation). Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status < 2; estimated life expectancy of at least 12 months; adequate haemato- logical function (absolute neutrophil count > 3000/mm3, haemoglobin 10 g/dL; platelet count > 150/mm3); and a negative pregnancy test and use of effective contraception in women of childbearing potential. Pre-treatment 18F-FDG PET/CT scans were performed as part of the screening process. Patients with Vesicovaginal and vesicorectal fistulas; extra- pelvic visceral metastases, and bilateral hydronephrosis visualised on screening 18F-FDG PET/CT scans, were excluded from the study, as were HIV-positive patients with a CD4 count < 200 cells/µL and/or not on antiretroviral therapy (ART) for at least six months and/or signs of ART resistance; contradictions or a known hypersensitivity to any of the prescribed treatments; life-threatening Acquired Immunodeficiency Syndrome (AIDS) defining illnesses (other than cervical carcinoma); prior invasive malignancy, other than LACC, diagnosed within the past 24 months; and pregnant or breast feeding women. For the analyses in this report, all participants who met the eligibility criteria, were randomised, were treated, and for whom data were available at two years and three years post-treatment, were included. Participants who were lost to follow-up are reported as “LTFU” and their last known disease status is included.

Treatment: As per institutional protocols, all participants received 50 Gy of external beam radiotherapy (EBRT) in 25 fractions, administered to the whole pelvis, using 2D planning with virtual simulation. High Dose Rate (HDR) brachytherapy (BT) (source used: Iridium-192), was administered in three fractions of 8 Gy for a total equivalent dose in 2 Gy fractions (for an alpha-beta ratio of 10) of 86 Gy. Further details of the RT method can be found in the paper by Minnaar et al. [27]. 2D planning for EBRT and HDR BT is standard in our facility and in resource-constrained settings due to the lack of access to sophisticated imaging techniques and due to limited resources and staff capacity available to manage the high volume of gynaecological oncology patients seen each year. All participants were prescribed two doses of 80 mg/m2 cisplatin, administered 21 days apart (according to the institutional protocol), during EBRT (not administered on BT days or mEHT days). Participants in the study group received two mEHT treatments per week (Model: EHY2000+; Manufacturer: Oncotherm GmbH, Troisdorf, Germany), with a minimum of 48 h in between mEHT treatments, at a target power of 130 W for a minimum of 55 min. The EBRT was started within thirty minutes of completing mEHT treatments. Total Kilojoules administered per treatment were recorded.

Randomisation and Masking: After enrolment, participants were randomly assigned (stratum: HIV status; accounting for age and stage), to receive CRT alone, or in combination with mEHT, using the REDCap stratified secure online random-sampling tool. Although the trial was open-label, and participants were aware of which group they were in due to the challenges associated with setting up a sham hyperthermia treatment, physicians reporting on the pre- and six month post-treatment 18F-FDG PET/CT scans were blinded to the group that the participants were in, as were the clinicians conducting the follow-up evaluations. Data Collection and Management: The research coordinator was responsible for collecting the data and data were captured using the online REDCap electronic data capture tool hosted by the University of the Witwatersrand. The treatments were administered and the clinical evaluations were conducted by the clinical team, without the involvement of the research coordinator.

Outcomes: The primary outcome was Two Year OS. Two year DFS, defined as the time from the start of treatment until the time of first documented disease recurrence, is also reported. The first evaluation of LDC

was done at six months post-treatment. If local disease was still visible on the six month 18F-FDG PET/CT, then DFS was considered a failure from day one and the number of days spent disease free was considered to be zero. Three year OS and DFS are also reported. The DFS was censored for cancer specific deaths. Participants who demised with a disease free status, and who did not demise from a treatment related death, before the two or three year cut off, were allocated a positive disease free status at the exit date and the exit date was recorded as the date of death. Late toxicity was graded according the Common Toxicity Criteria for Adverse Events (CTCAE) version 4, and Quality of life (QoL) was measured using the validated European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ): C30 and Cx24 (cervical cancer specific). The QLQs were available in several local languages [30] and were administered at one and two years post-treatment. The results were compared to the baseline QLQ results and the scoring and reporting were done in accordance with the EORTC guidelines [31,32]. According to the EORTC guidelines, the scores were converted linearly to scores from 0–100, where a high score represents higher functioning or a higher symptom experience, and a lower score represents a lower symptom experience or a lower functioning [33]. Early toxicity and QoL at six months post treatment have been previously reported [27,28]. A CEA was performed, and the outcome was Cost per Quality Adjusted Life Year (QALY). After initial treatment costs, only disease progression and hospitalization costs are further incurred in the model. The private healthcare model included costs associated with Intensity-Modulated Radiation Therapy (IMRT), weekly cisplatin and a broader range of chemotherapy drugs for recurrent or residual disease, whereas the public healthcare model included only 3D-planning for radiotherapy, two doses of cisplatin during RT, and limited treatment options for recurrent or residual disease.

Statistical Analysis: The sample size was calculated based on the estimated required sample sizes for a two-sample comparison of survivors' functions at two years (statistical power of 90%). We estimated an expected reduction in mortality at two years of 50%, based on OS of 20% in the Control Group and 40% in the experimental group. The statistical significance is defined as a two-sided alpha < 0.05 for a log-rank test, with a constant Hazard Ratio (HR) of 0.5693. Cox proportional hazards models including each factor (treatment group, HIV status, age, stage of the disease) were performed to compare the time from the start of treatment to the first occurrence of any event (death or disease recurrence). We report the HR; Odds Ratio (OR), and 95% confidence interval. Log-rank statistics were used to compare both treatment arms with Kaplan–Meier survival curves plotted at two and three years (for OS; DFS), for stage IIB and stage III participants separately and combined. Overall type I error was considered at 5%, and the survival analysis was done by intention to treat. The initial survival analysis was planned for two years post-treatment. However, the positive results seen at two years post-treatment motivated an extension of the follow- up to five years post-treatment. In this paper, we therefore include the original planned two year analysis as well as the three year analysis, which was used for the evaluation of the cost effectiveness. Late toxicity was graded according to the CTCAE V.4 for bone, renal, bladder, skin, subcutaneous tissues, mucous membranes and gastrointestinal systems. The frequency of reported grade 1/2 late toxicity and grade 3/4 toxicity were compared by treatment group and by HIV status using frequency tables. Pearson's Chi squared test and Fisher's exact tests were used to determine the difference in frequencies between groups. Multivariable proportional hazards regression models were used to identify significant predictors (including arm, HIV status, and number of cisplatin doses), of grades 3/4 late toxicity. Two-sample independent t-tests with equal variances were used to evaluate QoL score change from baseline to 12 and 24 months post-treatment between the two treatment groups. The differences in score changes between the groups are assessed using paired t- tests. STATA 15.0 Statistics software program (Stata Corporation, College Station, TX, USA) was used to analyse the data.

The CEA was performed with a time horizon of three years, using a Markov model with a six month cycle length, from the perspective of a private healthcare funder (medical aid scheme), and a public healthcare funder (the state). The two-tiered healthcare system in South Africa is comprised of a state-funded public healthcare system and a private healthcare system that is mostly funded by private contributions to medical aid schemes. An estimated 70–80% of the population makes use of the public healthcare system [34], and this setting is underfunded and poorly equipped to manage the large volume of patients. The input costs of the treatments for the public healthcare CEA are based on the direct costs to the state for the treatments, as outlined in by the Department of Health [35], and therefore represents the cost versus benefit of the treatment of patients in a public healthcare facility, funded by the state. The input costs of the treatments in the private healthcare CEA include the regulated profit added to the cost of the treatments, charged by the privately owned hospitals and by the healthcare professionals in private practice, to the private medical aid schemes. The results of the private healthcare CEA therefore represent the costs to the private healthcare funders, versus the clinical benefit of the members or patients.

3. Results

3.1. Participants

A total of 271 patients were screened between January 2014 and November 2017, and 210 eligible participants were enrolled and randomised (mEHT Group: n = 106, Control Group: n = 104). Five participants were lost to follow-up either before, during, or immediately after treatment (mEHT Group: n = 3, Control Group: n = 2) and were excluded from OS and DFS analyses. Four participants were lost to follow-up after treatment and could not be contacted (mEHT: one lost to follow-up at six-, nine-, and 18 months post- treatment; Control group: one lost to follow-up at 24 months post-treatment). These participants were excluded from the survival analysis, and their last recorded disease status and follow-up date were used for the DFS analyses (Figure 1). There were no significant differences in participant characteristics and treatment characteristics between the mEHT and Control groups (Tables 2 and 3). Two thirds of the participants had FIGO Stage III disease and half of all the participants were HIV-positive with more than two thirds of the HIV-participants in the under 50 years old age group. The median age was 50.1 (27.3–74.8), and 79% of participants were unemployed. The median RT dose received was 74 Gy (range: 2–74) and the average dose of cisplatin received was 131 mg/m2 per participant, with 12% of participants not receiving any cisplatin. In the mEHT Group, 97% of participants received 80% (8/10), or more of the prescribed mEHT treatments, with only 2% receiving 20% (2/10) or less of the prescribed mEHT treatments. All participants with a haemoglobin value < 10 g/dL at enrolment were transfused before treatment.

3.2. Two Year Survival

Survival data were available for 202 participants at two years post-treatment, (mEHT Group: n = 100; Control Group: n = 102), of which 53 [53%] and 43 [42%] participants in the mEHT Group and Control Group, respectively, were alive at the last follow-up. The frequency of participants achieving two year OS in the group with LDC at six months post- treatment (42/59 [71.2%]) was significantly higher than those who did not achieve LDC (17/59 [28.8%]; Pearson Chi2: p < 0.001). Local Disease Control is a significant predictor of two year OS (OR: 3.8; p < 0.001; 95%CI: 2.00–7.34). The risk of death was 30% lower in the mEHT group (HR: 0.70; p = 0.074; 95%CI: 0.48–1.03, adjusted for HIV status, age and FIGO stage) (Table 4, Figure 2a).

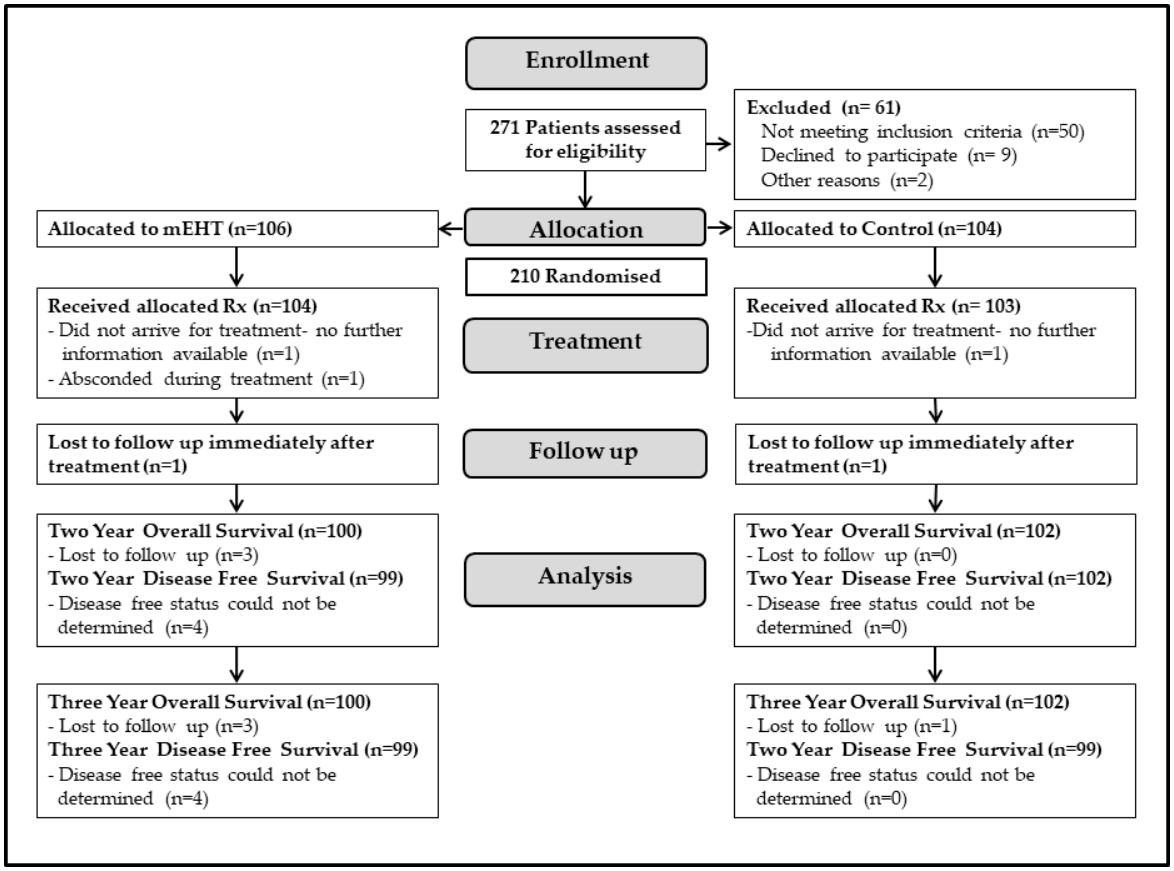


Figure 1. Trial profile. Abbreviations: mEHT: modulated electro-hyperthermia.

Table 2. Participant characteristics

Participant Characteristic		mEHT		Control		*p*-Value
		106	(50.5%)	104	(49.5%)	
HIV Status	Positive	52	(49.1%)	55	(52.9%)	$p = 0.579$
	Negative	54	(50.9%)	49	(47.1%)	
Age Group	<50 years	52	(49.1%)	46	(44.2%)	$p = 0.483$
	≥50 years	54	(50.9%)	58	(55.8%)	
ECOG	0	3	(2.8%)	7	(6.7%)	$p = 0.184$
	1	103	(97.2%)	97	(93.3%)	
Race	African	98	(92.5%)	97	(93.3%)	$p = 0.335$
	Caucasian	4	(3.8%)	1	(1.0%)	
	Indian	0	(0.0%)	0	(0.0%)	
	Asian	0	(0.0%)	0	(0.0%)	
	Mixed Race	4	(3.8%)	6	(5.8%)	
Education	Primary	45	(43.3%)	50	(49.0%)	$p = 0.334$
	Secondary	55	(52.9%)	51	(50.0%)	
	Tertiary	4	(3.8%)	1	(1.0%)	
Employment	Unemployed	83	(78.3%)	82	(78.8%)	$p = 0.923$
	Employed	23	(21.7%)	22	(21.2%)	

Table 2. Cont

Participant Characteristic		mEHT		Control		*p*-Value
		106	(50.5%)	104	(49.5%)	
FIGO Staging	IIB	40	(37.7%)	36	(34.6%)	$p = 0.895$
	IIIA	1	(0.9%)	1	(1.0%)	
	IIIB	65	(61.3%)	67	(64.4%)	
Histological Grade	1	7	(6.9%)	4	(4.1%)	$p = 0.759$
	2	70	(69.3%)	67	(69.1%)	
	3	24	(23.8%)	26	(26.8%)	
Tumour Dimensions (cm)	Median	7		7.1		$p = 0.1429$
	Min	2.7		1.8		
	Max	11.7		14.87		
Tumour SUV	Median	18.07		19.26		$p = 0.7769$
	Min	7.01		6.07		
	Max	63.25		97		
HB (g/dL)	Median	10.9		11		$p = 0.9424$
	Min	5.7		5.2		
	Max	16.2		16.2		
Age	Median	49.2		50.6		$p = 0.3665$
	Min	27.3		29.2		
	Max	70.8		74.8		
BMI	Median	27		26.5		$p = 0.3883$
	Min	15		15		
	Max	49		41.7		

Abbreviations: BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HB: Haemoglobin; HIV: Human Immunodeficiency Virus; mEHT: Modulated Electro-Hyperthermia; SUV: Standard Uptake Value.

Table 3. Treatment characteristics

Treatment		mEHT		Control		*p*-Value
Characteristics		106	(50.5%)	104	(49.5%)	
No of HDR BT doses	0	0	(0.0%)	0	(0.0%)	$p = 0.223$
	1	0	(0.0%)	2	(2.0%)	
	2	3	(2.9%)	1	(1.0%)	
	3	101	(97.1%)	99	(97.1%)	
No of Cisplatin Doses	0	14	(13.6%)	11	(10.7%)	$p = 0.727$
	1	42	(40.8%)	47	(45.6%)	
	2	47	(45.6%)	45	(43.7%)	
Total RT Dose	Median	74		74		$p = 0.6133$
	Min	20		2		
	Max	74		74		
Days between enrolment and Treatment	Median	37		37		$p = 0.2241$
	Min	18		21		
	Max	79		104		
No of mEHT doses	Median	10				
	Min	1				
	Max	10				

Abbreviations: HDR BT: High Dose Rate Brachytherapy; mEHT: Modulated Electro-Hyperthermia; RT: Radiotherapy.

Table 4. Multivariable Cox proportional hazards model for two year overall survival.

Overall	HR	*p*-Value	[95%CI]
mEHT	0.70	0.074	0.48–1.03
HIV-negative	0.82	0.328	0.54–1.23
Age at Enrolment	0.97	*0.007*	0.95–0.99
FIGO Stage III	1.01	0.785	0.71–1.57
FIGO Stage II	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.88	0.677	0.47–1.64
HIV-negative	0.73	0.342	0.37–1.41
Age at Enrolment	0.99	0.401	0.96–1.02
FIGO Stage III	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.61	0.047	0.37–0.99
HIV-negative	0.90	0.699	0.54–1.52
Age at Enrolment	0.96	0.006	0.94–0.99

Abbreviations: FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; mEHT: Modulated Electro-Hyperthermia.

When considering participants with Stage II and Stage III disease separately, the risk of death within two years post-treatment, adjusted for age, disease stage, and HIV status, was significantly lower in the mEHT participants with Stage III disease compared to the Control participants with Stage III disease (mEHT Group: 34/61 [56%]; Control Group: 27/67 [40%]; HR: 0.61; p = 0.047; 95%CI: 0.37–0.99). Age was also a significant predictor of two year OS in the group of participants with Stage III disease (HR: 0.96, p = 0.006, 95%CI: 0.94–0.99) (Table 4).

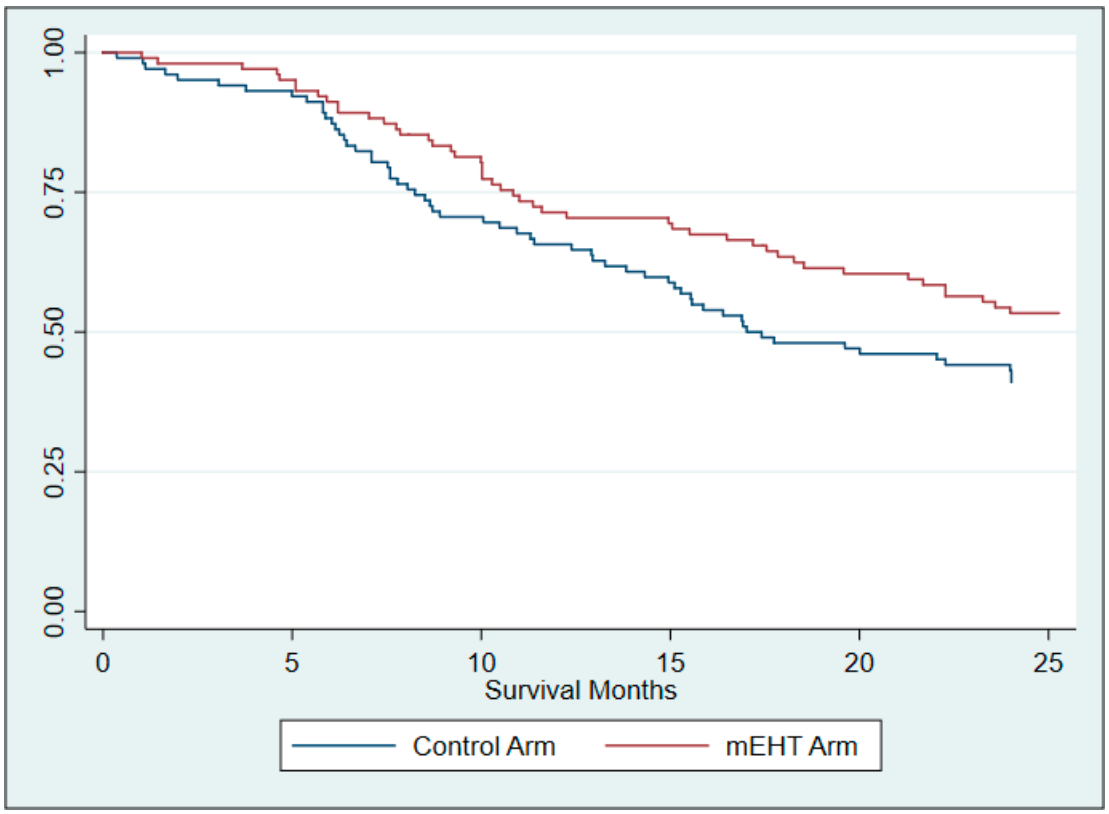
When analysing the sample by treatment arm, age was a significant predictor of two year OS in the mEHT Group (HR: 0.95, p = 0.001, 95%CI: 0.93–0.98), but not in the Control Group (HR: 0.98, p = 0.181, 95%CI: 0.96–1.01). We subsequently analysed participants according to their age group at the time of randomization (30 years; 30–50 years; >50 years). As there were only three participants younger than 30 years, we combined them with the group of participants between 30 and 50 years. Considering the participants younger than 50 years, and 50 years and older separately, the addition of mEHT had the most significant effect on two year OS in the age group 50 years and above (HR: 0.44, p = 0.011, 95%CI: 0.24–0.83).

Two year DFS was seen significantly more frequently in the mEHT Group (36/99 [36.4%]) than in the Control Group (14/102 [13.7%]; p < 0.0001), with participants treated with mEHT having 33% less risk of developing a

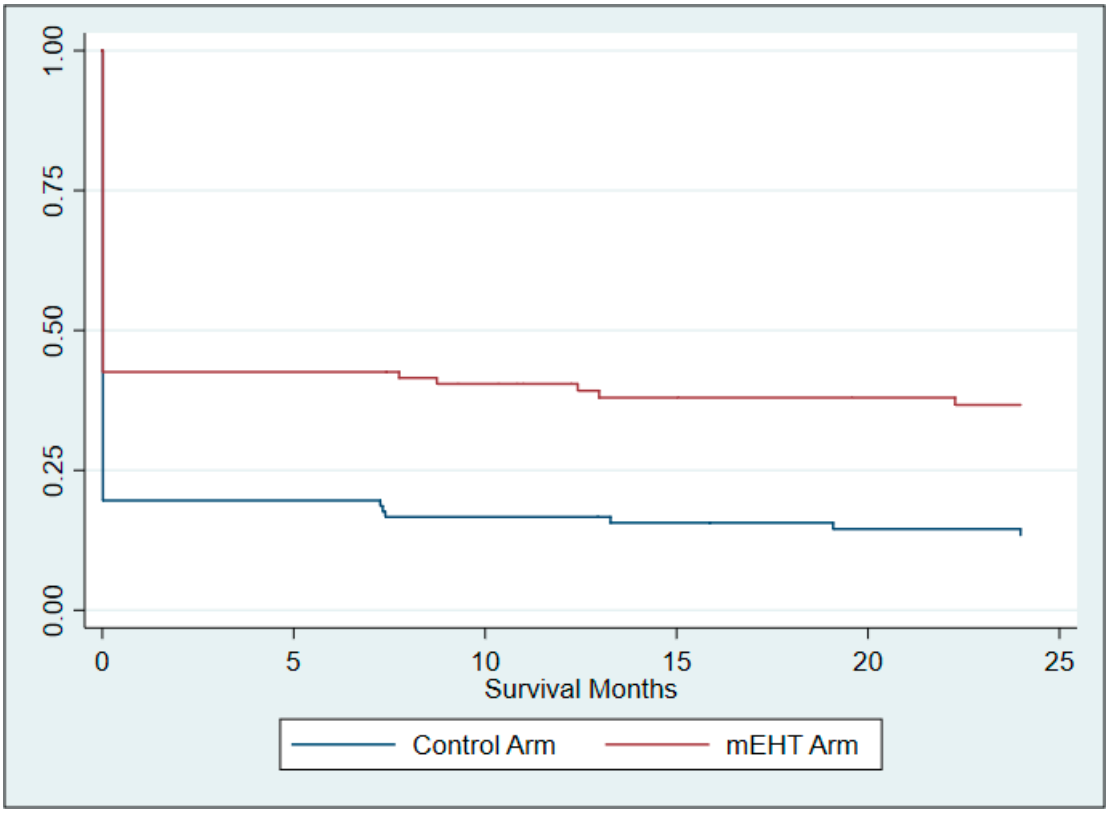
recurrence during the first two years than the Control Group participants (HR: 0.67, 95%CI: 0.48–0.93. p = 0.017, adjusted for age, stage, and HIV status) (Table 5, Figure 2b). Participants treated with mEHT had an odds ratio of 3.59 of achieving disease free status at two years (p < 0.001; 95%CI: 1.79–7.21) compared to Control Group participants. When evaluated by disease stage, mEHT was not significantly predictive of two year DFS in participants with Stage II disease but remained significant for participants with Stage III disease (Table 5).

3.3. Three Year Survival

Three year OS was achieved by 33.7% (34/101) and 44% (44/100) of participants from the Control and mEHT Groups, respectively. The risk of death in the first three years was 28% lower for the participants who received mEHT, although this was not significant (HR: 0.72; 95%CI: 0.51–1.03, p = 0.74; adjusted for age, disease stage and HIV status) (Figure 3a), and when considering only the participants with Stage III disease, the risk was significantly lower (38%) in the mEHT group (HR: 0.62; p = 0.040; 95%CI: 0.40–0.98, adjusted for age, and HIV status) (Table 6).



(a)



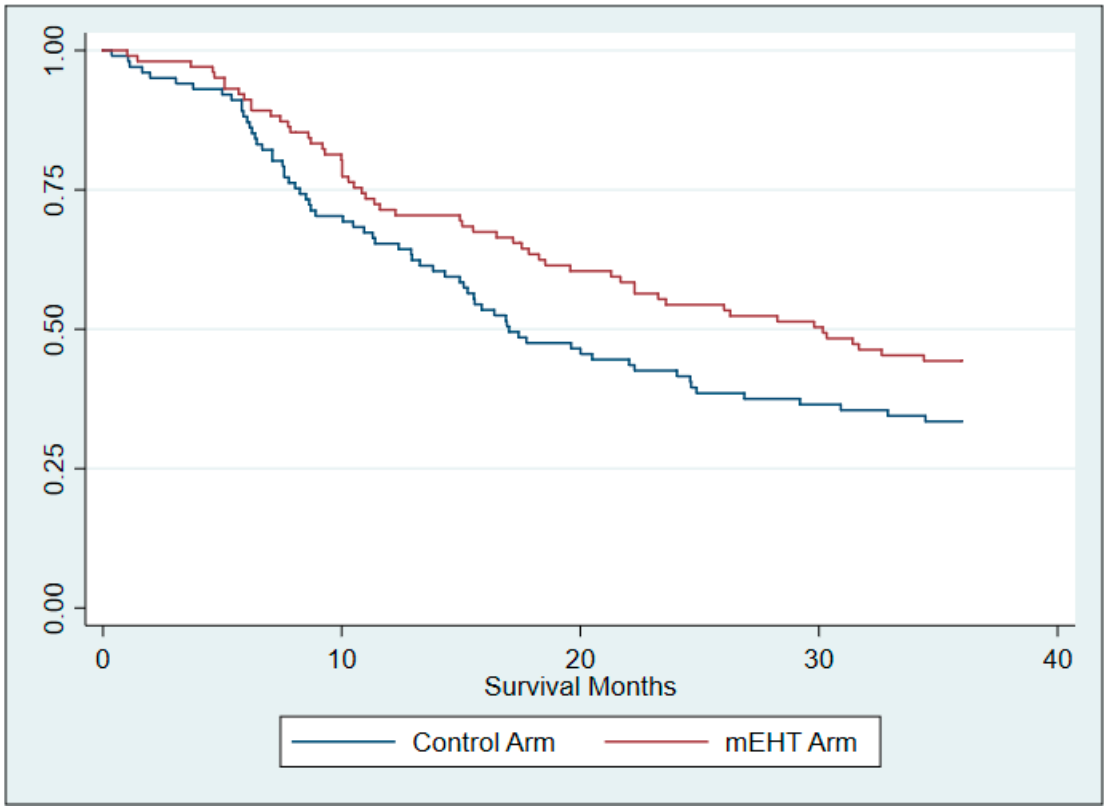
(b)

Figure 2. Kaplan–Meier survival curves at two years (a) two year overall survival; (b) two year disease free survival. The sharp drop of the DFS rates seen early on in 2b is a result of the higher rate of residual disease at six months post-treatment in the Control Group compared to mEHT Group. Participants with residual disease post-treatment were considered to have zero disease free survival days.

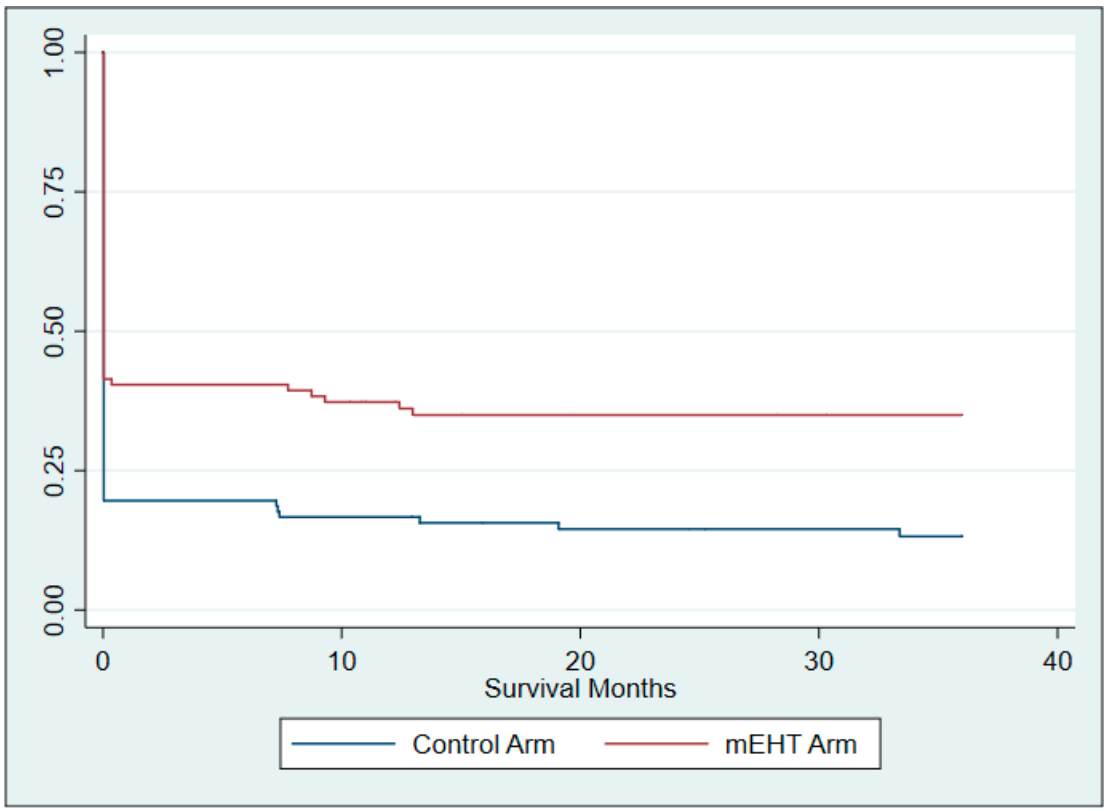
Table 5. Multivariable Cox proportional hazards model for two year disease free survival.

Overall	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.67	0.017	0.48–0.93
HIV-negative	0.99	0.257	0.72–1.48
Age at Enrolment	0.99	0.257	0.97–1.01
FIGO Stage III	0.99	0.944	0.79–1.38
FIGO Stage II	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.77	0.342	0.45–1.32
HIV-negative	1.18	0.569	0.66–2.01
Age at Enrolment	0.99	0.601	0.97–1.02
FIGO Stage III	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.62	0.025	0.41–0.94
HIV-negative	0.98	0.915	0.97–1.01
Age at Enrolment	0.99	0.301	0.97–1.01

Abbreviations: FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; mEHT: Modulated Electro-Hyperthermia.



(a)



(b)

Figure 3. Kaplan–Meier survival curves at three years (a) three year overall survival; (b) three year disease free survival. The sharp drop off in DFS rates seen early on in 3b is again a result of the high rate of residual disease at six months post treatment.

The frequency of DFS remained significantly higher in the mEHT Group compared to the Control Group at three years post-treatment (mEHT: 35/99 [35.4%]; Control: 14/102 [13,7%]; Chi-squared: p < 0.0001) with an odds ratio of 3.4 of achieving DFS in favour of the mEHT Group (p = 0.001; 95%CI: 1.71–6.91) and a hazard ratio of 0.70 (95%CI: 0.51–0.97; p = 0.035, adjusted for age, stage and HIV status) (Figure 3b). When evaluated by stage of disease, the significance remained in participants with Stage III disease (Table 7).

Table 6. Multivariable Cox proportional hazards model for three year overall survival.

Overall	HR	*p*-Value	[95%CI]
mEHT	0.72	0.074	0.51–1.03
HIV-negative	0.84	0.366	0.58–1.23
Age at Enrolment	0.98	*0.019*	0.96–1.00
FIGO Stage	1.10	0.619	0.76–1.59
FIGO Stage II	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.91	0.748	0.51–1.64
HIV-negative	0.75	0.365	0.40–1.40
Age at Enrolment	0.99	0.468	0.96–1.02
FIGO Stage III	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.62	*0.040*	0.40–0.98
HIV-negative	0.93	*0.777*	0.58–1.50
Age at Enrolment	0.97	*0.018*	0.95–0.99

Abbreviations: FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; mEHT: Modulated Electro-Hyperthermia.

Table 7. Multivariable Cox proportional hazards model for three year disease free survival.

Overall	HR	*p*-Value	[95%CI]
mEHT	0.70	0.035	0.51–0.98
HIV-negative	1.05	0.786	0.74–1.50
Age at Enrolment	0.99	0.240	0.97–1.01
FIGO Stage	0.98	0.913	0.70–1.37
FIGO Stage II	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.78	0.357	0.46–1.33
HIV-negative	1.20	0.538	0.68-2.11
Age at Enrolment	0.99	0.582	0.97–1.02
FIGO Stage III	**HR**	***p*-Value**	**[95%CI]**
mEHT	0.66	0.040	0.43–0.98
HIV-negative	0.98	0.932	0.62–1.55
Age at Enrolment	0.99	*0.278*	0.97–1.01

Abbreviations: FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; mEHT: Modulated Electro-Hyperthermia.

3.4. Late Toxicity

There was no significant difference in frequencies of reported late toxicity (grouped according to grades I/II and grades III/IV), between the two treatment groups or between the HIV-positive and HIV–negative participants at 9 months, 12 months, 18 months, and 24 months post-treatment. Multivariate Cox proportionate hazards models, including arm, HIV status and cisplatin doses, did not show any significant predictors of grades I/II or grades III/IV late toxicity.

3.5. Quality of Life

There were no statistically significant differences in QLQ scores between the two groups at baseline assessment [28]. When comparing the changes in scores from baseline to 24 months between groups, the reduction in pain was significantly higher in the mEHT Group (p = 0.0368), cognitive function was significantly improved in the mEHT group (p = 0.0044), and participants in the Control Group reported a reduction in role functioning while the mEHT Group participants reported an improvement in role functioning with a significant difference between the two groups (p = 0.0172). When assessing the change from baseline to 12 months within each group, there was an improvement in all scales except for role functioning in the mEHT Group, with significant improvements in Global Health Scale, Pain, Fatigue, and Emotional functioning. In the Control Group, there were significant improvements in the Visual Analogue Scale, Global Health Scale, Nausea and Vomiting, and Emotional Functioning, while Physical Functioning, Role Functioning and Cognitive Functioning decreased in the Control Group (Table 8). When assessing the change from baseline to 24 months within each group, the mEHT group reported a significant improved of all scales except for role function (which improved by a score of 9.4), while the Control Group only reported a significant change in five out of 11 scales, with a negative change in cognitive function (Table 9).

Table 8. Mean change in scores from baseline to 12 months in the mEHT and Control Group.

12 Months	mEHT				Control			
	Mean	SD	95%CI	*p*-Value	Mean	SD	95%CI	*p*-Value
Visual Analogue	5.4	31.6	−2.9 to 13.8	$p = 0.1961$	9.7	29.8	2.1 to 17.3	$p = 0.0133$
Global Health	10.2	34.3	1.2 to 19.2	$p = 0.0275$	13.8	36.3	4.4 to 23.1	$p = 0.0047$
Financial Burden	−7.1	50.7	−207 to 6.4	$p = 0.2967$	−6.1	48.0	−19.1 to 7.0	$p = 0.3537$
Symptom Scales								
Pain Reduction	−18.4	37.3	−28.2 to −8.6	$p = 0.0004$	−6.3	40.2	−16.6 to 4.0	$p = 0.2264$
Nausea/Vomiting	−5.5	23.4	−11.6 to 0.7	$p = 0.0815$	−6.5	19.1	−11.4 to −1.7	$p = 0.0094$
Fatigue reduction	−9.4	31.0	−17.5 to −1.2	$p = 0.0247$	−1.3	40.5	−11.6 to 9.1	$p = 0.8065$
Functional Scales								
Social	5.5	46.9	−6.9 to 17.8	$p = 0.3787$	2.6	55.2	−12.0 to 17.3	$p = 0.7201$
Cognitive	7.5	31.9	−0.9 to 15.9	$p = 0.0795$	−1.1	34.0	−10.1 to 7.3	$p = 0.7542$
Emotional	9.8	31.9	1.4 to 18.2	$p = 0.0233$	13.4	39.9	3.2 to 23.6	$p = 0.0111$
Role	−3.2	40.9	−13.9 to 7.6	$p = 0.5583$	−4.9	40.0	−15.2 to 5.3	$p = 0.3401$
Physical	2.3	29.9	−5.6 to 10.2	$p = 0.5599$	−4.0	27.7	−11.2 to 3.1	$p = 0.2594$

Abbreviations: CI: Confidence Interval; mEHT: Modulated Electro-Hyperthermia; SD: Standard Deviation.

Table 9. Mean change in scores from baseline to 24 months in the mEHT and Control Group.

	mEHT				Control			
	Mean	SD	95%CI	*p*-Value	Mean	SD	95%CI	*p*-Value
Visual Analogue	25.1	21.5	16.6 to 33.6	$p < 0.0001$	15.6	31.9	2.9 to 28.2	$p = 0.0176$
Global Health	23.2	31.7	11.7 to 35.6	$p = 0.0002$	17.3	29.1	6.0 to 28.6	$p = 0.0041$
Financial Burden	−26.1	60.9	−48.0 to 4.1	$p = 0.0216$	−16.7	46.7	−34.8 to 1.4	$p = 0.0698$
Symptom Scales								
Pain Reduction	−34.4	32.8	−46.2 to −22.6	$p = 0.0001$	−15.5	35.7	−29.3 to −16	$p = 0.0298$
Nausea/Vomiting	−13.0	27.7	−23.0 to −3.0	$p = 0.0122$	−1.2	18.7	−8.4 to 6.1	$p = 0.7383$
Fatigue reduction	−18.4	27.9	−28.5 to −8.4	$p = 0.0008$	−10.7	34.0	−23.9 to 2.4	$p = 0.1071$
Functional Scales								
Social	12.0	31.2	0.7 to 23.2	$p = 0.0375$	17.3	41.7	1.1 to 33.4	$p = 0.0373$
Cognitive	19.8	33.2	7.8 to 31.6	$p = 0.0020$	−4.2	28.9	−15.4 to 7.0	$p = 0.4523$
Emotional	27.3	30.3	16.4 to 38.3	$p < 0.0001$	17.9	34.2	4.6 to 31.1	$p = 0.0101$
Role Function	9.4	35.1	−3.3 to 22.1	$p = 0.1415$	7.1	35.0	6.4 to 20.7	$p = 0.2893$
Physical	11.7	21.2	4.0 to ‘9.3	$p = 0.0040$	2.6	27.2	−7.9 to 13.2	$p = 0.6150$

Abbreviations: CI: Confidence Interval; mEHT: Modulated Electro-Hyperthermia; SD: Standard Deviation.

3.6. The Abscopal Effect

We previously reported on an increased frequency of an abscopal effect seen in the mEHT participants at six months post-treatment [29]. The three year follow-up of these participants shows that 10 of the 14 mEHT participants with an abscopal effect were disease free at three years post-treatment, and three participants

were deceased, two of whom were disease free at death (cause of death renal failure, DFS days 335 and 596), and one whom was disease free at the last follow-up with an unknown cause of death after 860 days. Of the three participants in the Control Group who had an abscopal response, two achieved three year DFS and one demised after 483 days, due to renal failure. The disease pattern and description of these participants are detailed in our previous paper on the abscopal effect seen at six months post-treatment [29].

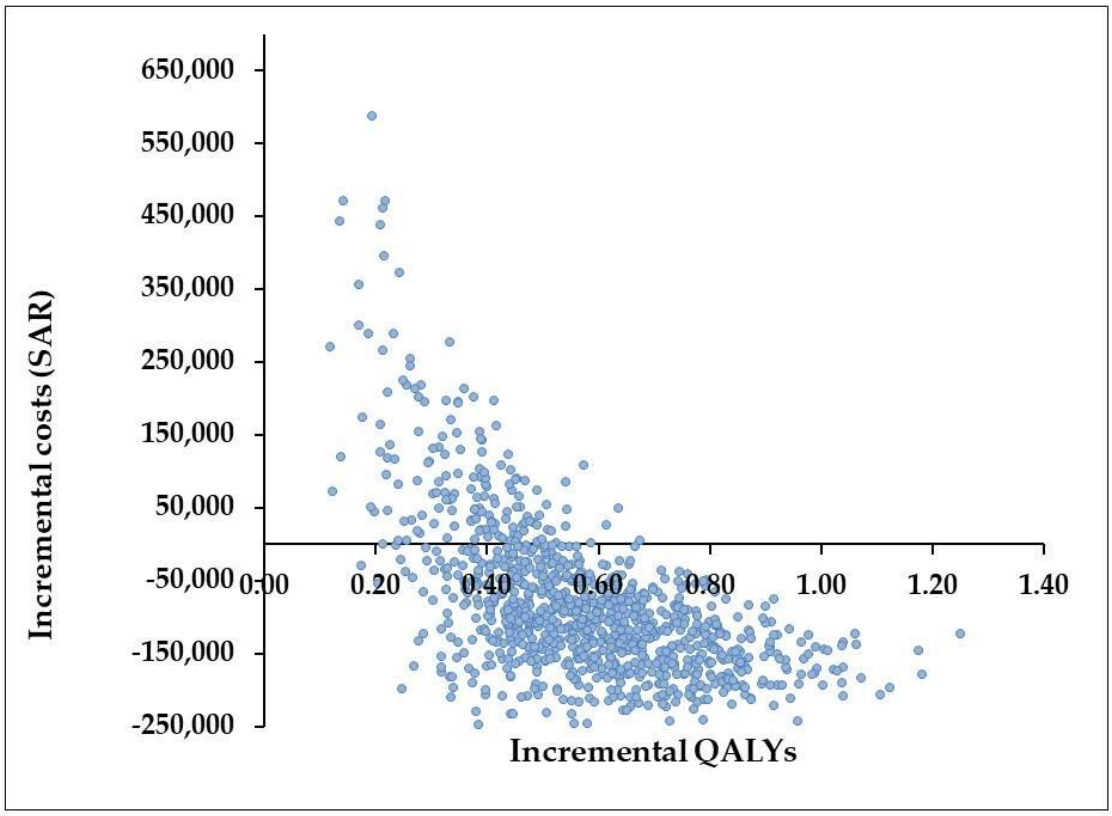
3.7. Cost Effectiveness Analysis

The addition of mEHT to CRT increases the efficacy of the oncology treatments; however, it also increases the initial input costs. The base case CEA showed that the addition of mEHT to CRT dominated the model, compared to CRT alone, making the combined treatment (mEHT + CRT) less costly and more effective, from the perspective of both government and private healthcare funders. This result is driven by the difference in DFS and is due to the high costs of recurrent and progressive disease. This model did not use a societal costing perspective, which incorporates productivity-loss costs as well as dying costs, especially before retirement age. The incremental cost-effectiveness ratio (ICER) plane shows that CRT + mEHT produces more health effects at a lower cost over three years, in the government and private healthcare model, per disease free cycle (a half year lived in perfect health) (Figure 4). The probability that mEHT + CRT is cost-effective compared with CRT alone is about 82.2% in the government healthcare model and 77.7% in the private healthcare model, at no additional cost. The QALYs are summarised in Table 10.

Table 10. Quality adjusted life year data for private and government healthcare CEA models.

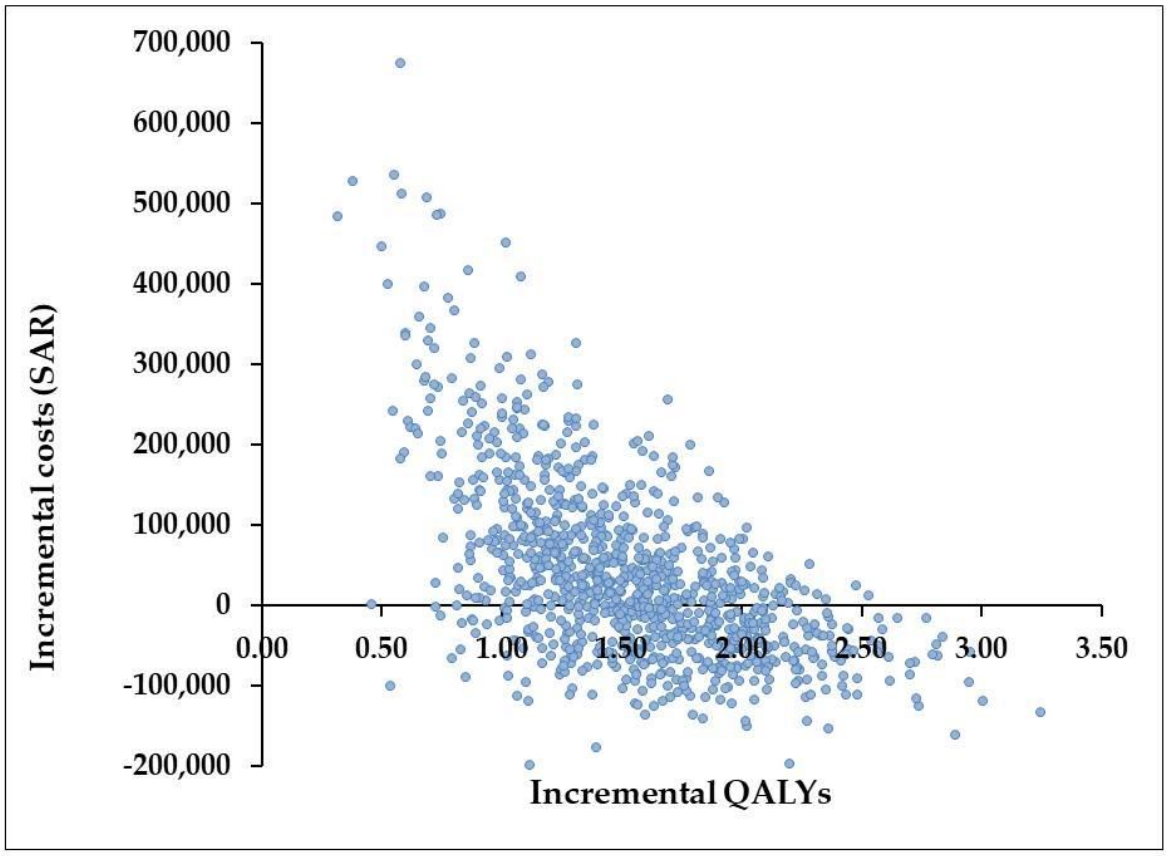
Perspective	Treatment	Cost in ZAR	QALYs Gained *	Incremental Cost	Incremental QALYs *	ICER
Government	mEHT	412,433.37	4.84			
	CRT	449,290.02	4.60	36,836.65	−0.24	Dominated
Private payer	mEHT	579,998.97	4.84			
	CRT	617,421.79	4.60	37,422.82	−0.24	Dominated

* QALYs gained in the two perspectives are the same since assumptions for health effects were the same. The only differences in the model inputs were the costs.



(a)

Figure 4. Cont.



(b)

Figure 4. Incremental cost-effectiveness ratio (ICER) plane (a) government healthcare model; (b) private healthcare model. The Cost Effectiveness Analysis was done for both a Government-funded and a privately-funded healthcare model, for the same duration (three years), assuming the same health effects, with the only difference being the input costs. In the Government-funded healthcare model, the QALYs range from 0–1.4, with incremental costs mainly seen in the 4th Quadrant, showing improved clinical benefits and lower costs per QALY with the addition of mEHT. In the Privately funded healthcare model, the QALYs range from 0–3.5 with incremental costs falling in the lower portion of the 1st quadrant and the upper portion of the 4th quadrant, implying a clinical benefit with a high probability of cost saving with the addition of mEHT to chemoradiotherapy.

4. Discussion

The results from this study show a significant improvement in two and three year DFS with the addition of mEHT to CRT protocols for LACC, without any significant changes in late toxicity. This follows our previous paper describing the improvement in LDC with the addition of mEHT to CRT. The strict criteria for LDC evaluation is one of the strengths of the study. Evaluation of LDC was based on pre- and post-treatment 18F-FDG PET/CT scans, examinations, and fine needle aspiration if indicated. Local disease control was considered a failure if any disease was confirmed in the pelvis [27]. We previously described the safety of mEHT in our paper on early toxicity, and reported high compliance rates to mEHT treatments in our high risk population. Other strengths of the study include the low variability in patient and treatment characteristics between the groups, the strict control between the groups, and the low number of participants lost to follow-up, even in the resource-constrained setting.

Our sample included HIV-positive participants, who are expected to have worse outcomes [36–38], and overweight participants [28]. Radiobiological data have previously suggested that HIV-positive patients may be more radiosensitive, and may therefore be at risk of increased toxicity from RT [39,40]. The evaluation of the early and late toxicity associated with RT combined with mEHT as a radiosensitiser in HIV-positive patients is therefore important in our setting where around 50% of LACC patients are HIV-positive. Heating pelvic tumours using capacitive HT techniques carries a high risk of adipose burns, especially when the treatment area includes a layer of adipose tissue thicker than 1.5 cm [41,42]. The safety demonstrated by mEHT for the management of cervical cancer, even in participants with above average BMIs, alongside the efficacy, indicates that mEHT is able to effectively and safely target deep tumours that would otherwise be

difficult to treat using conventional capacitive HT. Factors which may contribute to the improved safety and efficacy of mEHT include the lower power output of mEHT (maximum of 130 W in our study), compared to other capacitive HT devices, the non-thermal effects [14] or field effects [16,43], and the AM of the RF waves in mEHT, which appears to contribute to the improved selectivity and enhanced effects in the tumour [18,25].

We initially estimated a reduction in two year mortality of 50% in order to achieve a power of 90% based on our sample size. While two year OS rates were not significantly improved, the reduction in disease recurrence at two years in the mEHT group was significant and was more than 50% (36.4% DFS in the mEHT Group and only 13.7% DFS in the Control Group), giving a statistical power of >90% for the DFS assessment. The effect of mEHT on outcomes was seen more significantly in the two year and three year DFS analyses than in the OS analyses, and the significance remained in both the HIV-positive and -negative participants and when considering participants based on age category. However, the significance was lost when considering only the participants with Stage II disease. In the OS analyses, the significance of the effects of mEHT on outcomes was less consistent. This may be a result of the inclusion of non-cancer related deaths in the OS analysis, which likely masked the effects of mEHT in the OS analyses. In our sample, the majority of the HIV-positive participants were younger than 50 years, and this may contribute to the improved OS outcomes seen in participants over the age of 50 years, compared to those younger than 50 years. This suggests that, while mEHT still improves the OS of HIV-positive participants, the effect is higher in HIV-negative participants as seen in the older group containing mostly HIV-negative women. In the group of participants who were 50 years and older, mEHT was a consistently significant predictor of DFS, regardless of HIV-status.

A limitation of the study is the substandard RT and BT administered as a result of a lack of sophisticated imaging and planning techniques in our setting, compared to developed settings. Due to resource constraints, the standard of care weekly cisplatin schedule was also not prescribed. Other limiting factors related to resource constraints include time to start EBRT, time to complete RT, and time between treatment completion and 18F-FDG PET/CT scans. Delays were most frequently attributed to technical problems, machine down-time, and source supply problems (in the case of the 18F-FDG PET/CT scans), as previously reported [27]. Another limitation of the study is the apparent high rate of under-staging of the patients using clinical staging techniques. The participants were all staged according to the recommended FIGO staging guidelines from 2014, and the institutional protocols at the time, using a chest X-ray, abdomino-pelvic ultrasound, and examination. The FIGO staging system was revised in 2018 to include more sophisticated imaging techniques which are able to include lymph node involvement and to improve the accuracy of the staging. The earlier FIGO staging criteria resulted in up to 40% of stage IB-IIIB cases being under diagnosed and as many as 64% of stage IIIB cases being over-diagnosed [44]. Funding was obtained for the addition of 18F-FDG PET/CT scans pre-treatment and six months post-treatment to assess clinical response to treatment. The 18F-FDG PET/CT scans were therefore not used for staging purposes in our study; however, participants with visceral and bone metastases and bilateral hydronephrosis on the 18F-FDG PET/CT scans were still excluded as they required a change in the treatment protocol. The pre-treatment 18F-FDG PET/CT scans indicated that more than half of the patients were in stage IVB disease, as seen by the high number of patients with extra-pelvic nodal involvement and local invasion of the bladder and rectum that was not detected during the routine clinical staging procedures. In a sub-group analysis of these participants, it was noted that there was complete metabolic resolution of all diseases, local and distant, in around a quarter of those who received mEHT. This suggests that mEHT may potentiate the abscopal effect induced by ionising radiation. This also provided an opportunity to assess the systemic effects of mEHT. The previously reported abscopal results [29], combined with the long term follow-up of the abscopal response reported in this paper, suggest that the preclinical immunological effects, observed in response to the administration of mEHT [45–47], could have clinical benefits in the management of systemic disease as well as local disease. If we consider that Stage IVB disease is generally considered incurable, then a disease free status in the participants with extra-pelvic disease at three years of 24.5% in
the mEHT group compared to the 5.6% in the control group, even with sub-optimal RT delivery, is a significant and important outcome.

Only one Phase III study has investigated CRT with/without classical HT (using capacitive HT), for the management LACC, and they reported an improvement in five year DFS from 60.6% (95%CI, 45.3–72.9%) to 70.8% (95%CI, 55.5–81.7%), although the difference was not significant (HR: 0.517, 95%CI, 0.251–1.065, p = 0.073) [48]. While results from Phase III studies on RT with/without classical HT are positive, they are not comparable to our study, due to the differences in HT techniques and treatment protocols. Classical HT requires a substantial increase in local temperature in order to slow down DNA repair and induce tumour cell killing [12], and thermo-monitoring is a critical safety and efficiency measure [10], while mEHT aims to improve perfusion and support an immune response to the tumours [49], with a mild temperature increase, and without the need for thermo- monitoring as a measure of safety and efficiency.

The substantial improvements in quality of life are an important result to consider as prolonged life is not always associated with quality of life in cancer patients. The adverse effects from oncology treatments can negatively impact the quality of life even in patients who are disease free, while persistent and recurrent disease are often considered to be poor predators of quality of life. An increase in life expectancy, together with a decreased quality of life and increased costs of treatment for adverse effects and persistent/recurrent disease, can place additional burden on the healthcare system. The CEA performed confirms that the improvement in quality of life, and improvement in DFS, not only benefits the patients and the community, but also has the potential to reduce the economic burden of the disease in both private and public healthcare settings.

While it is unclear how much of an effect mEHT as a radiosensitiser would have when added to optimal RT and BT delivery for cervical cancer, it is encouraging to see such a large improvement in two and three year DFS with the addition of mEHT, even in sub- optimal conditions and in our high-risk population. There is still room for improvement in five year OS rates in cervical cancer patients with stage III and IV disease globally, even with sophisticated RT techniques, and a safe and effective radiosensitiser, such as mEHT, may still be a beneficial adjunct to RT in optimal settings. The continued monitoring of participants in the reported study will provide more insight into the effects of mEHT on five year survival. Modulated electro-hyperthermia is a feasible addition to LACC treatment protocols to improve outcomes, especially in settings in which sophisticated imaging and RT technologies are not accessible.

5. Conclusions

Modulated electro-hyperthermia enhances outcomes of LACC patients when added to CRT, without increasing the toxicity profile of treatments. The associated improvement in quality of life along with the reduction in healthcare costs makes this intervention a feasible and effective adjunct to CRT for the management of LACC. The addition of mEHT improved LDC and DFS in our sample, without additional toxicity, and with improved role functioning of the patients, benefiting both the patients, the community, and the already-strained healthcare system. Modulated electro-hyperthermia could therefore be considered as an adjunct to CRT, especially in resource-constrained settings and for cervical cancer patients with advanced disease. The five year follow-up results and detailed CEA will provide further insight into the long term benefits of mEHT as an adjunct to CRT. Further investigations into the immunological effects of mEHT could assist in the long-term goal of shifting RT from a local treatment, to a systemic treatment when combined with mEHT, offering additional options for patients with metastatic disease. Studies on the systemic effects of mEHT, as well as studies with the aim of better understanding the thermal and non-thermal effects of mEHT, are likely to shed more light on the mechanisms of action and further improve the application and recommendations for the use of mEHT in a clinical setting.

Author Contributions
Conceptualization, J.A.K. and C.A.M., methodology, J.A.K. and C.A.M.; software, C.A.M.; validation, A.B. and C.A.M.; formal analysis, I.M. and C.A.M.; investigation, C.A.M. and J.A.K.; resources, A.B. and J.A.K.; data curation, C.A.M.; writing—original draft preparation,
C.A.M. and I.M.; writing—review and editing, C.A.M., I.M., J.A.K. and A.B.; visualization, J.A.K.,
A.B. and C.A.M.; supervision, A.B. and J.A.K.; project administration, A.B.; funding acquisition, J.A.K. All authors have read and agreed to the published version of the manuscript.

Funding
This research was funded by the National Research Foundation, Grant No. TP12082710852, awarded to J.A. Kotzen. The funder did not have any involvement in the protocol development, data collection, data analysis, or reporting.

Institutional Review Board Statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the Charlotte Maxeke Johannesburg Academic Hospital and the Human Research and Ethics Committee of the University of the Witwatersrand on 4 May 2012 (M120477), and renewed on 5 May 2017 (M704133).

Informed Consent Statement
Informed consent was obtained from all subjects involved in the study.

Data Availability Statement
The data presented in this study will be made openly available in (repository name e.g., FigShare) upon acceptance of the paper for review.

Acknowledgments
The modulated electro-hyperthermia device was sponsored by Oncotherm GMBh, for the duration of the trial. 18F-FDG was supplied at a reduced rate by NTP Radioisotopes SOC. The Radiation Oncology and Nuclear Medicine Department and all supportive staff involved in the patient care and management at the hospital at which the study took place, Charlotte Maxeke Jo- hannesburg Academic Hospital, are acknowledged. We acknowledge and thank all of the participants, without whom this study would not be possible, who showed courage, grace, and determination throughout their journey, despite the difficulties that were faced with this under-resourced and poor socio-economic setting.

Conflicts of Interest
The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References
1. International Agency for Research on Cancer. Cancer Today; GLOBOCON: Lyon, France, 2020. Available online: https://gco.iarc. fr/today/home (accessed on 21 January 2022).
2. Arbyn, M.; Weiderpass, E.; Bruni, L.; De Sanjosé, S.; Saraiya, M.; Ferlay, J.; Bray, F. Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. Lancet Glob. Health 2020, 8, 191–203. [CrossRef]
3. Denny, L.; Anorlu, R. Cervical Cancer in Africa. Cancer Epidemiol. Biomark. 2012, 21, 1434–1439. [CrossRef] [PubMed]
4. Ghebre, R.G.; Grover, S.; Xu, M.J.; Chuang, L.T.; Simonds, H. Cervical cancer control in HIV-infected women: Past, present and future. Gynecol. Oncol. Rep. 2017, 21, 101–108. [CrossRef] [PubMed]
5. Horsman, M.R.; Overgaard, J. Hyperthermia: A Potent Enhancer of Radiotherapy. Clin. Oncol. 2007, 19, 418–426. [CrossRef]
6. Datta, N.R.; Rogers, S.; Klingbiel, D.; Gomez, S.; Puric, E.; Bodis, S. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: A systematic review with conventional and network meta-analyses. Int. J. Hyperth. 2016, 6736, 809–821. [CrossRef]
7. Van Der Zee, J.; González González, D. The Dutch Deep Hyperthermia trial: Results in cervical cancer. Int. J. Hyperth. 2002, 18, 1–12. [CrossRef]
8. Franckena, M.; Stalpers, L.J.A.; Koper, P.C.M.; Wiggenraad, R.G.J.; Hoogenraad, W.J.; van Dijk, J.D.P.; Wárlám-Rodenhuis, C.C.; Jobsen, J.J.; van Rhoon, G.C.; van der Zee, J. Long-Term Improvement in Treatment Outcome After Radiotherapy and Hyperthermia in Locoregionally Advanced Cervix Cancer: An Update of the Dutch Deep Hyperthermia Trial. Int. J. Radiat. Oncol. Biol. Phys. 2008, 70, 1176–1182. [CrossRef]

9. Harima, Y.; Nagata, K.; Harima, K.; Ostapenko, V.V.; Tanaka, Y.; Sawada, S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int. J. Hyperth. 2001, 17, 97–105. [CrossRef]
10. Franckena, M.; Fatehi, D.; de Bruijne, M.; Canters, R.A.; van Norden, Y.; Mens, J.W.; van Rhoon, G.C.; van der Zee, J. Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur. J. Cancer 2009, 45, 1969–1978. [CrossRef]
11. Kroesen, M.; Mulder, H.T.; van Holthe, J.M.; Aangeenbrug, A.A.; Mens, J.W.M.; van Doorn, H.C.; Paulides, M.M.; Oomen-de Hoop, E.; Vernhout, R.M.; Lutgens, L.C.; et al. Confirmation of thermal dose as a predictor of local control in cervical carcinoma patients treated with state-of-the-art radiation therapy and hyperthermia. Radiother. Oncol. 2019, 140, 150–158. [CrossRef]
12. Crezee, H.; Kok, H.P.; Oei, A.L.; Franken, N.A.P.; Stalpers, L.J.A. The impact of the time interval between radiation and hyperthermia on clinical outcome in patients with locally advanced cervical cancer. Front. Oncol. 2019, 9, 412. [CrossRef] [PubMed]
13. Kroesen, M.; Mulder, H.T.; van Rhoon, G.C.; Franckena, M. Commentary: The Impact of the Time Interval Between Radiation and Hyperthermia on Clinical Outcome in Patients With Locally Advanced Cervical Cancer. Front. Oncol. 2019, 9, 1387. [CrossRef] [PubMed]
14. Wust, P.; Kortüm, B.; Strauss, U.; Nadobny, J.; Zschaeck, S.; Beck, M.; Stein, U.; Ghadjar, P. Non-thermal effects of radiofrequency electromagnetic fields. Sci. Rep. 2020, 10, 13488. [CrossRef] [PubMed]
15. Fiorentini, G.; Szasz, A. Hyperthermia today: Electric energy, a new opportunity in cancer treatment. J. Cancer Res. Ther. 2006,
2, 41. [CrossRef] [PubMed]
16. Andocs, G.; Renner, H.; Balogh, L.; Fonyad, L.; Jakab, C.; Szasz, A. Strong synergy of heat and modulated electromagnetic field in tumor cell killing. Strahlenther. Onkol. 2009, 185, 120–126. [CrossRef]
17. Yang, K.L.; Huang, C.C.; Chi, M.S.; Chiang, H.C.; Wang, Y.S.; Hsia, C.C.; Andocs, G.; Wang, H.E.; Chi, K.H. In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia. Oncotarget 2016, 7, 84082–84092. [CrossRef]
18. Wust, P.; Ghadjar, P.; Nadobny, J.; Beck, M.; Kaul, D.; Winter, L.; Zschaeck, S. Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia. Int. J. Hyperth. 2019, 36, 1246–1254. [CrossRef]
19. Tsang, Y.W.; Huang, C.C.; Yang, K.L.; Chi, M.S.; Chiang, H.C.; Wang, Y.S.; Andocs, G.; Szasz, A.; Li, W.T.; Chi, K.H. Improving immunological tumor microenvironment using electro-hyperthermia followed by dendritic cell immunotherapy. BMC Cancer 2015, 15, 708. [CrossRef]
20. Andocs, G.; Meggyeshazi, N.; Okamoto, Y.; Balogh, L.; Szasz, O. Bystander Effect of Oncothermia. Conf. Pap. Med. 2013,
2013, 953482. [CrossRef]
21. Meggyeshazi, N.; Andocs, G.; Balogh, L.; Balla, P.; Kiszner, G.; Teleki, I.; Jeney, A.; Krenacs, T. DNA fragmentation and caspase- independent programmed cell death by modulated electrohyperthermia. Strahlenther. Onkol. 2014, 190, 815–822. [CrossRef]
22. Andocs, G.; Meggyeshazi, N.; Balogh, L.; Spisak, S.; Maros, M.E.; Balla, P.; Kiszner, G.; Teleki, I.; Kovago, C.; Krenacs, T. Upregulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modulated electrohyperthermia. Cell Stress Chaperones 2015, 20, 37–46. [CrossRef] [PubMed]
23. Szasz, O.; Szigeti, P.G.; Vancsik, T.; Szasz, A. Hyperthermia Dosing and Depth of Effect. Open J. Biophys. 2018, 8, 31–48. [CrossRef]
24. Papp, E.; Vancsik, T.; Kiss, E.; Szasz, O. Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (mEHT). Open J. Biophys. 2017, 7, 216–229. [CrossRef]
25. Lee, S.-Y.; Kim, J.-H.; Han, Y.-H.; Cho, D.-H. The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma. Int. J. Hyperth. 2018, 34, 953–960. [CrossRef] [PubMed]
26. Szasz, A.M.; Minnaar, C.A.; Szentmártoni, G.; Szigeti, G.P.; Dank, M. Review of the Clinical Evidences of Modulated Electro- Hyperthermia (mEHT) Method: An Update for the Practicing Oncologist. Front. Oncol. 2019, 9, 1012. [CrossRef] [PubMed]
27. Minnaar, C.A.; Kotzen, J.A.; Ayeni, O.A.; Naidoo, T.; Tunmer, M.; Sharma, V.; Vangu, M.D.T.; Baeyens, A. The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial. PLoS ONE 2019, 14, e0217894. [CrossRef] [PubMed]
28. Minnaar, C.A.; Kotzen, J.A.; Naidoo, T.; Sharma, V.; Vangu, M.; Baeyens, A.; Anne, C.; Kotzen, J.A.; Naidoo, T. Analysis of the effects of mEHT on the treatment- related toxicity and quality of life of HIV-positive cervical cancer patients. Int. J. Hyperth. 2020, 37, 263–272. [CrossRef]
29. Minnaar, C.A.; Kotzen, J.A.; Ayeni, O.A.; Vangu, M.; Baeyens, A. Potentiation of the Abscopal Effect by Modulated Electro- Hyperthermia in Locally Advanced Cervical Cancer Patients. Front. Oncol. 2020,

10, 376. [CrossRef]
30. Koller, M.; Aaronson, N.K.; Blazeby, J.; Bottomley, A.; Dewolf, L.; Fayers, P.; Johnson, C.; Ramage, J.; Scott, N.; West, K. Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach. Eur. J. Cancer 2007, 43, 1810–1820. [CrossRef]
31. Fayers, P.; Bottomley, A. Quality of life research within the EORTC—The EORTC QLQ-C30. Eur. J. Cancer 2002, 38, S125–S133.
[CrossRef]
32. Aaronson, N.; Ahmedzai, S.; Bergman, B.; Bullinger, M.; Cull, A.; Duez, N.; Filiberti, A.; Flechtner, H.; Fleishman, S.; de Haes, J.; et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J. Natl. Cancer Inst. 1993, 85, 365–376. [CrossRef] [PubMed]
33. Fayers, P.; Aaronson, N.; Bjordal, K.; Groenvold, M.; Curran, D.; Bottomley, A. The EORTC QLQ-C30 Scoring Manual, 3rd ed.; European Organisation for Research and Treatment of Cancer: Brussels, Belgian, 2001.
34. Department of Statistics South Africa. General Household Survey; Pretoria, South Africa, 2021; Volume P0318. Available online: http://www.statssa.gov.za/publications/P0318/P03182020.pdf (accessed on 21 January 2022).
35. National Department of Health South Africa. Uniform Patient Fee Schedule 2020; Pretoria, South Africa, 2020. Available online: https://www.health.gov.za/uniform-patient-fee-schedule/ (accessed on 21 January 2022).
36. Coghill, A.E.; Newcomb, P.A.; Madeleine, M.M.; Richardson, B.A.; Mutyaba, I.; Okuku, F.; Phipps, W.; Wabinga, H.; Orem, J.; Casper, C. Contribution of HIV infection to mortality among cancer patients in Uganda. AIDS 2013, 27, 2933–2942. [CrossRef]
37. Coghill, A.E.; Shiels, M.S.; Suneja, G.; Engels, E.A. Elevated cancer-specific mortality among HIV-infected patients in the United States. J. Clin. Oncol. 2015, 33, 2376–2383. [CrossRef] [PubMed]
38. Dryden-Peterson, S.; Bvochora-Nsingo, M.; Suneja, G.; Efstathiou, J.A.; Grover, S.; Chiyapo, S.; Ramogola-Masire, D.; Kebabonye-Pusoentsi, M.; Clayman, R.; Mapes, A.C.; et al. HIV Infection and Survival Among Women With Cervical Cancer. J. Clin. Oncol. 2016, 34, 3749–3761. [CrossRef]
39. Herd, O.; Francies, F.; Kotzen, J.; Smith, T.; Nxumalo, Z.; Muller, X.; Slabbert, J.; Vral, A.; Baeyens, A. Chromosomal radiosensitivity of human immunodeficiency virus positive / negative cervical cancer patients in South Africa. J. Mol. Med. Rep. 2016, 13, 130–136. [CrossRef] [PubMed]
40. Baeyens, A.; Slabbert, J.P.; Willem, P.; Jozela, S.; Van Der Merwe, D.; Vral, A. Chromosomal radiosensitivity of HIV positive individuals. Int. J. Radiat. Biol. 2010, 86, 584–592. [CrossRef] [PubMed]
41. Kok, H.P.; Crezee, J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. Int. J. Hyperth. 2017, 33, 378–386. [CrossRef]
42. D'Ambrosio, V.; Dughiero, F. Numerical model for RF capacitive regional deep hyperthermia in pelvic tumors. Med. Biol. Eng. Comput. 2007, 45, 459–466. [CrossRef]
43. Andocs, G.; Rehman, M.U.; Zhao, Q.-L.; Tabuchi, Y.; Kanamori, M.; Kondo, T. Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells. Cell Death Discov. 2016, 2, 16039. [CrossRef]
44. Lee, S.I.; Atri, M. 2018 FIGO staging system for uterine cervical cancer: Enter cross-sectional imaging. Radiology 2019, 292, 15–24. [CrossRef]
45. Vancsik, T.; Forika, G.; Balogh, A.; Kiss, E.; Krenacs, T. Modulated electro-hyperthermia induced p53 driven apoptosis and cell cycle arrest additively support doxorubicin chemotherapy of colorectal cancer in vitro. Cancer Med. 2019, 8, 4292–4303. [CrossRef] [PubMed]
46. Vancsik, T.; Kovago, C.; Kiss, E.; Papp, E.; Forika, G.; Benyo, Z.; Meggyeshazi, N.; Krenacs, T. Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts. J. Cancer 2018, 9, 41–53. [CrossRef] [PubMed]
47. Jeon, T.W.; Yang, H.; Lee, C.G.; Oh, S.T.; Seo, D.; Baik, I.H.; Lee, E.H.; Yun, I.; Park, K.R.; Lee, Y.H. Electro-hyperthermia up-regulates tumour suppressor Septin 4 to induce apoptotic cell death in hepatocellular carcinoma. Int. J. Hyperth. 2016, 32, 648–656. [CrossRef] [PubMed]
48. Harima, Y.; Ohguri, T.; Imada, H.; Sakurai, H.; Ohno, T.; Hiraki, Y.; Tuji, K.; Tanaka, M.; Terashima, H. A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer. Int. J. Hyperth. 2016, 32, 801–808. [CrossRef] [PubMed]
49. Szasz, O.; Szasz, A. Heating, Efficacy and Dose of Local Hyperthermia. Open J. Biophys. 2016, 6, 10–18. [CrossRef]

Review on the Use of Modulated Electro-Hyperthermia as a Stand-Alone Therapy in a Palliative Setting: Potential for Further Research?

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Cite this article as:
Minnaar, C.A. et al. (2022): Review on the Use of Modulated Electro-Hyperthermia as a Stand-Alone Therapy in a Palliative Setting: Potential for Further Research? Journal of Cancer Therapy, 13, 362-377.
https://doi.org/10.4236/jct.2022.136032

Oncothermia Journal 32, September 2022: 95 – 105.
www.oncotherm.com/sites/oncotherm/files/2022-09/Minnaar_Review_on_mEHT_as_standalone_therapy.pdf

Abstract:
Background: Hyperthermia (HT) in oncology was originally applied as a stand-alone treatment (monotherapy), but achieving temperatures required to cause cellular destruction (>43˚C) proved to be challenging. Lower temperatures may increase the risk of dissemination of the treated tumours. Hyperthermia in the current context of oncology therefore aims to achieve moderate temperatures of 39˚C - 41.5˚C and is applied in combination with chemotherapy (ChT) and/or radiotherapy (RT). Modulated electro-hyperthermia (mEHT) applies amplitude modulation to an electric field generated by a capacitive coupled set-up, to selectively heat tumours. As mEHT does not ap- pear to increase the risk of disease dissemination, it has been investigated as a stand-alone treatment for patients with advanced disease and who have exhausted all other treatment options. This report is a descriptive review of pa- pers in oncology which report on the use of mEHT as a stand-alone treatment in a palliative setting. We aim to establish whether there is motivation for the development of trials to further investigate mEHT as a monotherapy in a palliative setting.
Methods: A literature search was conducted using the key words "Oncothermia", "modulated electro-hyperthermia" and "monotherapy", and case reports were excluded. Only studies which applied mEHT without ChT or RT; for palliative intent; when conventional therapies have failed; or when no further options are available, were included.
Results: Six phase I/II studies on tumours of the liver, brain, pancreas, and stomach were included. The studies demonstrated the safety of mEHT; disease stabilisation; and improved quality of life.
Conclusion: mEHT may have a role in the palliative management of certain tumours in the absence of any other treatment options. The development of robustly designed studies on mEHT for palliative management of oncology patients is motivated.

Keywords:
Modulated Electro-Hyperthermia, Palliative Care, Monotherapy, Cancer

1. Introduction

Investigations into the thermal sensitivity of tumours (both spontaneous and induced), date back to as early as 1903 [1] [2] and it is now well-known that tumour cells have a higher sensitivity to heat than their healthy counterparts. This variation in thermal sensitivity is also observed between different tumour cell lines [3] [4] [5]. Hyperthermia (HT) in the current context of oncology refers to the moderate (39˚C - 41.5˚C) heating up of tumours in order to sensitise them to the prescribed treatment regimens [6]. The dose control, protocols, and thermometry vary depending on the heating technique applied. Hyperthermia was however originally applied as a monotherapy with the treatment goal of inducing temperatures of ≥43˚C, resulting in the direct damage and destruction of the tumour cells [1] [2].

Positive results using HT as a monotherapy were presented at the International Symposium on Hyperthermic Oncology in Kyoto in 1988 [7]. In 1990, Gabriele et al. published a paper on the use of HT (microwave or radiofrequency) as a monotherapy for 60 superficial recurrent tumours. A complete response (CR) was noted in 10 (16.6%) tumours and a partial response (PR) in 14 (23.4%) tumours [8]. In a phase I study on superficial recurrent tumours, Manning et al. demonstrated a local response following treatment with HT alone. However the same study demonstrated that the combination of HT and external beam radiation (EBRT) yielded superior results [8]. Sannazzari et al. reported similar results in their study on HT (using microwave heating), with or without EBRT for the management of locally recurrent breast cancer [9]. The use of radiofrequency (RF) heating techniques in HT can be traced as far back as the 1930s [10] with initial reports showing positive results following the application of RF-HT as a stand-alone therapy [11] [12] [13].

Despite the positive results, there have been some obstacles. The high temperatures required to induce direct cellular damage frequently cause damage to the surrounding healthy tissues and result in hot spot formation [14]. Achieving cytotoxic temperatures in tumours using the currently available technology is challenging [15]. A handful of studies have shown that the local response does not always result in an increased survival time and it has even been suggested that heating the tumour and increasing the blood flow may increase the risk of dissemination of the tumour [16] [17].

In combination with chemotherapy (ChT) or radiotherapy (RT), HT has however continued to show improved outcomes for a range of malignancies [18] [19]. When combined with other treatment modalities, the risk of disseminated disease appears to be reduced [18] [20] [21]. Interest in HT as a monotherapy has subsequently declined and HT is now almost exclusively applied synergistically with RT or ChT. Most studies show an improved local control with no significant difference in toxicity when HT is added to either RT or ChT [10] [18] [19]. However in at least one study, no difference in local control was reported and higher (although not

significantly), acute and late toxicity was reported in the group treated with HT plus RT compared to RT alone [22]. Although the benefits of HT combined with RT or ChT on local disease control are widely documented, a at least two studies have shown questionable survival benefitsm[23] [24] [25]. Discrepancies in results have been attributed to variations in techniques and thermometry [26] and to the lack of a temperature reference point [27].

Several mechanisms of sensitisation to ChT and RT by HT have been de- scribed. At temperatures ranging from 39˚C - 42˚C, HT interferes with protein synthesis [28] and inhibits DNA and RNA synthesis and repair [28] [29]. Hyperthermia therefore complements RT and certain cytotoxic drugs which cause DNA double-strand breaks, by inhibiting the repair of the breaks [30] [31] [32]. Increased blood perfusion seen at temperatures between 38˚C and 42˚C increases oxygen and drug delivery to the tumour [15], however at temperatures of 43˚C and above, vasoconstriction occurs and oxygen perfusion declines [33]. Moderate HT (<43˚C) therefore provides another mechanism of radio-sensitisation as hypoxia plays a central role in radio-resistance [33] [34]. Additionally, the failure of DNA replication and repair in the S-phase of the cell cycle, caused by the application of HT, results in mitotic catastrophe [33]. Hyperthermia there- fore also has the potential to sensitise the otherwise more radio- and chemo-resistant cells in the S-phase of the cell cycle to the damaging effects of RT and certain cytotoxic agents [18]. Hyperthermia promotes the release of intra-cellular Heat Shock Protein 70 (HSP70) into the extracellular matrix where it is involved in a complex cascade of reactions triggering a local and systemic immune response to the malignant cells [35]. Frey et al. describe the immunomodulating mechanisms of HT involving the extracellular HSP70 which has an epitope that acts as a signal for Natural Killer (NK) cells, and leads to enhanced NK cell proliferation, migration, and killing activity [36]. Additionally HSP70 appears to play a role in the activation of the tumour suppressor gene p53 [37] [38] [39]. As a result of the immunomodulating effects of HT, the addition of HT to RT may promote the abscopal effect, an immune-mediated response following the local irradiation of a tumour that results in a systemic response to metastatic, non-irradiated lesions [18]. When combined with ChT, the increase in metabolism of the heated cells results in an increase in the reaction rate of the drugs [40]. The effects of HT on ChT does however depend largely on the type of ChT used [41].

This paper reviews the application of modulated electro-hyperthermia (mEHT) applied as a monotherapy with palliative intent. Modulated electro-hyperthermia is a widely used, mild-to-moderate (<41.5˚C) heating technique which utilises amplitude modulated (AM) RF (13.56 MHz) in a capacitive-coupled set up, with impedance matching [40]. The technique induces an increase in temperature high enough to improve perfusion [42], and to induce chemo- [42] and radio[43] sensitisation, safely, even in high risk populations [44]. Although the exact mechanisms of action are not currently fully understood, the improved out- comes despite the milder, and therefore safer, temperatures of mEHT are believed to be attributed to the AM of the carrier frequency, the effects of the electric field on the cell membranes [45] [46], and the subsequent modulating effects on the immune system [47] [48].

In vitro and in vivo murine experiments have demonstrated the tumour-killing effects and immune-modulating effects of mEHT as a monotherapy without the increased risks of metastases in murine models [45] [46] [49] [50] [51] [52] and have shown mEHT to be superior to conventional heating techniques when ap-plied at the same temperature [45] [46]. As a result of the safety and the ease with which treatments are applied, researchers have investigated mEHT applied as a monotherapy for palliative intent, in cases where no further treatment options are available. Numerous case studies have been published on the use of mEHT for the management of patients with locally advanced disease who have failed conventional treatments. The case studies report tumour regression and disease stabilisation for tumours of the colon, rectum, liver, pancreas, lung, bladder, ovaries, stomach, and kidneys [53].

The objective of this review is to explore the potential for mEHT to be applied as a monotherapy for palliative intent, when conventional therapies have failed, and when no further options are available. Examples of patients who may benefit from mEHT as a monotherapy, should it prove effective, include patients with organ failure, recurrent/resistant disease, treatment toxicity, and disease progression requiring palliative or supportive treatment.

2. Methodology

This is a descriptive review of studies published on the use of mEHT as a stand-alone therapy in oncology. Inclusion criteria: A literature search was con- ducted using the key words “Oncothermia”, “modulated electro-hyperthermia”, and “monotherapy” in PubMed. Only studies which applied mEHT as a mono- therapy for palliative intent; when conventional therapies have failed; or when no further options are available, were included. Exclusion criteria: Human, clinical case-reports have shown the potential for mEHT to be used as a

monotherapy [applied after failure of conventional treatments. For the purpose of this re- view however, case-studies were excluded. The literature search returned six studies eligible for inclusion in the review. The studies were on liver metastases (from colorectal cancer), primary liver tumours, brain tumours, pancreatic tumours and gastric tumours. All reviewed reports used the EHY2000+ (Oncotherm GmbH, Troisdorf, Germany) device.

3. Results

All of the studies, with the exception of the study on brain tumours, applied a step-down heating protocol. This involves applying a high power output at the start of the treatment, and reducing the power as the patient feels discomfort at the treatment site. This reduces the risk of dissemination by inducing a transient high temperature and causing vasoconstriction at the beginning of the treatment. The step-down heating method is described elsewhere in the literature [54] [55] [56]. Treatments to the brain applied a step-up heating protocol, as this is considered safer in more sensitive areas. Treatments were administered two to three times per week, with at least 48 hours in between treatments in order to prevent the development of thermo-tolerance [37] [57] [58] [59]. In the reviewed studies, the treatment duration depends on the size of the applicator used (30 cm applicator requires 60 minutes of treatment time and the 20 cm applicator requires a treatment time of up to 90 minutes, with the exception of head and neck treatments), and the treatment location. Sensitive areas such as the brain are treated for 45 - 60 minutes while areas with effective cooling mechanisms, such as the lung, require up to 90 minutes, regardless of the applicator size. Table 1

Location	*n*	Protocol	Treatment frequency
Liver metastases (colorectal primary) [60]	80	Step-down heating starting from 130 W, for 60 min	2/week; 8/cycle; cycles repeated every 5 - 6 weeks until dx progression
Liver primary [61]	8	80 W - 130 W for 60 min	2/week for 5 weeks.
Brain [62]	12	Step-up, starting at 40 W for 20 min; increasing linearly to 150 W for 60 min over 2 weeks	3/week for 8 wks followed by a CT, repeated until dx progression
Brain [63]	149	Step-up, starting at 40 W for 20 min; increasing linearly to 150 W for 60 min over 2 weeks	3/week for 8 wks followed by a CT, repeated until dx progression
Pancreas [64]	6	Step-up, starting at 60 W for 40 min; increasing linearly to 150 W for 90 min over 2 weeks.	3/week for 8 wks followed by a CT, repeated until dx progression
Gastric [65]	25	60 min	3/week

Table 1. Summary of protocols for mEHT applied as a monotherapy.
Abbreviations: CT: Computed Tomography dx: Disease; Min: Minutes; W: Watt; wks: weeks. summarises the protocols that were applied in the reported studies which used mEHT as a monotherapy.

3.1 Liver Metastases from Colorectal Cancer

Eighty participants, who had failed prior treatment, were enrolled in a single arm, prospective, phase II study evaluating mEHT treatments for the palliative management of liver metastases from colorectal cancer. Of the 80 participants, 36% (n = 29) also presented with extra-hepatic lesions. The cycle of mEHT treatments (described in Table 1), was repeated until disease progression was observed. Thirty seven percent (n = 30) of the participants were eligible for palliative chemotherapy during the follow up (median time to first chemotherapy dose: 4.5 months), and subsequently received 5-Fluorouracil + Folinic acid + Mitomycin-C. Long lasting disease stabilisation was noted with a median overall survival time of 24.1 months from the time of first diagnosis of metastases, and the administration of ChT did not significantly change the overall survival. Fifty one percent (n = 41) of participants survived two years and 31% survived three years, which, according to the authors' report, is significantly better than the expected survival rates of 36% and 19% respectively. The authors noted that the mild increase in temperature alone was unlikely to be responsible for the bene- fits seen in the sample, and hypothesised that the interactions with the electro- magnetic field may also contribute to the positive outcomes noted [60].

3.2 Hepatocellular Carcinoma

Ferrari et al. presented results on a phase II study investigating mEHT as a palliative treatment option for primary, chemo-refractory, hepatocellular carcinoma at the annual meeting of the American Society of Clinical Oncology in 2007. Twenty-two participants with non-resectable tumours were enrolled. Fourteen participants were eligible for retreatment with chemotherapy (Oxaliplatin: 50 mg/m2) and mEHT, and eight participants were treated only with mEHT. One cycle of treatment consisted of 10 mEHT treatments, administered twice per week for five weeks (treatment duration: 60 minutes), and the median number of cycles administered was 1.5 (range: 1 - 4). Four participants developed a skin reaction after mEHT with three developing a mild superficial burn which was treated with local steroids. The authors reported one complete response and stable disease in 25% of the participants, with a median survival time of 20.5 weeks (range: 5 - 81). Improved well-being was reported in 50% of the participants treated with mEHT and the authors concluded that mEHT was a safe modality which could be explored further for chemo-refractory hepatocellular carcinoma [61].

3.3 Brain

A phase II study on the application of mEHT for the management of 12 relapsed malignant glioma patients by Fiorentini et al., demonstrated the safety of mEHT to the brain. All participants were previously treated with RT and temozolamide (TMZ). Eight of the participants had glioblastoma multiforme (GBM), two had anaplastic astrocytoma grade III, and two had anaplastic oligodendroglioma. Adverse events reported were persistent head pain in one (8%) participant, mild burn on the scalp in one (8%) participant, and two (17%) participants experienced seizures that were successfully treated with dexamethasone, furosemide, mannitol, and diazepam. One complete remission and two partial remissions were achieved, with a response rate of 25% and a median duration of response of 10 months (range 4 - 32) [62].

Following the results of this 2006 study, Fiorentini et al. proceeded with a phase II, retrospective study investigating mEHT as a monotherapy treatment for relapsed malignant glioma and astrocytoma tumours, compared to best supportive care (BSC), involving dexamethasone, 18% glycerol infusion, mannitol, holistic therapy, and psychosocial support. The researchers enrolled 149 consecutive participants, of which 111 (74%) had GBM, and 38 (26%) had astrocytoma (AST). Palliative care using mEHT was administered to 28 (25%) GBM patients and 22 (58%) AST patients, and BSC was administered to 83 GBM and 14 AST participants. Tumour response was based on the RECIST, v.1.1 criteria and was evaluated by CT or magnetic resonance imaging (MRI) after three months of treatment. A tumour response of 29% and 48% of GBM and AST participants respectively was seen in the mEHT group, and 4% and 10% of GBM and AST patients respectively in the BSC group. The authors report a five-year overall survival of 83% in the AST participants treated with mEHT versus 25% in the participants treated with BSC. In the GBM group, the five-year survival was 3.5% after mEHT, versus 1.2% after BSC [63].

3.4 Pancreatic Cancer

Patients with stage III-IV pancreatic adenocarcinoma were retrospectively di- vided into two groups: those treated with mEHT and those who did not receive mEHT, in this multicentric observational study. Of the 34 participants treated with mEHT, six (15%) received only mEHT and the rest received ChT plus mEHT. Tumour response was evaluated at three months by CT or MRI studies. A total of 499 mEHT treatments were

administered. Adverse events included skin pain in 12 (2%) of the treatments, grade 1 burns in six (1%) of treatments, and grade 2 burns in two of the treatments. All adverse events were resolved within a week of discontinuing treatment. Of the 34 participants treated with mEHT, only two progressed (8%) compared to 23 (34%) in the non-mEHT group. The median overall survival of the mEHT group was 18.0 months (range: 1.5 - 68) and 10.9 months (range: 0.4 - 55.4 months) in the non-mEHT group [64].

3.5 Gastric Cancer

Modulated electro-hyperthermia was applied as a monotherapy to 25 patients with unresectable/recurrent gastric cancer. Outcomes evaluated were tumour volume, symptom experience, and performance. Nine patients had distant metastases on enrolment. Survival time in these nine patients was significantly better than an analysis of a matching retrospective historical arm. Patients treated with mEHT reported improved performance and symptom experience as well as a reduction in tumour size [65].

4. Discussion

This report discusses six phase I/II studies in which mEHT is applied as a monotherapy for some or all of the participants. The safety of mEHT treatments has been established in these studies and elsewhere in the literature when applied alone or when combined with ChT and/or RT [44] [66] [67] [68]. The risk of adverse events is low when applying mEHT in cases in which there are no further treatment options. The results suggest that patients with refractory disease, and in whom there are no further treatment options, may benefit from mEHT as a stand-alone treatment. The benefits may include disease stabilisation, palliation, and a prolonged overall survival. It is however difficult to draw definitive conclusions, due to the variation in study designs and the lack of data from a prospective, randomised controlled trial.

While some of the mechanisms of action of HT are applicable to mEHT, HT and mEHT have some fundamental differences in their effects on cells and tis- sues. This is largely attributed to the differences in temperature achieved and technology applied. Different HT techniques have different actions resulting in variations in outcomes [32] [46] [69]. The mechanisms of action of both mEHT and HT are however still not fully understood. When considering mEHT as a monotherapy, the temperature alone is unlikely to play a major role in the cellular destruction, given that the increase in temperatures seen during mEHT is- mild (achieving only fever-range temperatures) [55], and does not reach 43˚C (the temperature required to cause direct damage and necrosis to the cells). Several preclinical studies on mEHT have however shed light on the immune-related effects of mEHT. These effects include the induction of apoptosis [69], and of deoxyribonucleic acid (DNA) fragmentation, apoptotic bodies, and nuclear shrinkage, which further suggests the induction of programmed cell death pathways [70] [71]. The mEHT-induced programmed cell death appears to be mostly caspase-dependent [46] [49], but in HT29 murine xenografts an independent pathway was observed via the induction of apoptosis inducing factor (AIF) [70]. Modulated electro-hyperthermia triggers the release of damage associated molecular pattern (DAMP) proteins and results in an increase in the cell-membrane expression of HSP70 [49]. The release of HSP70 from cells into the extracellular environment [46] triggers an influx of antigen presenting dendritic cells and killer T-cells (CD8+) which are primed for the recognition of the malignant cells. This could contribute to a systemic immune response to the tumours [49] [71]. These immunogenic effects are believed to be due to the effect of the electromagnetic field and amplitude modulation on the membranes of tumour cells [32] [46] [72]. Minnaar et al. reported on the complete metabolic resolution of metastases outside of the treatment field in 24% (14/54) of participants treated with chemoradiotherapy and mEHT to the cervix in a phase III randomised controlledtrial [73]. These results further hint to the potential effect of mEHT on the immune response to metastatic disease, and the possibility that mEHT can potentiate immune-related effects of ionising radiation. In a three
year follow-up of the participants, 35/99 [35.4%] participants in the mEHT group were alive and disease free compared to 14/102 [13.7%] participants in the control group (OR: 3.4; 95% CI: 1.71 - 6.91l p = 0.001) [74].
The literature contains several case reports of spontaneous tumour regressions in the absence of any treatments [75] [76] [77]. Challis et al. reported on 489 cases of spontaneous regression described from 1900 to 1987 [78] and in 2001, Hobohm published an extended meta-analysis in which he suggested that the presence of feverish conditions in many of the spontaneous regressions indicates a link between immune stimulation and tumour regression [79]. In his paper,
Hobohm suggests the investigation into fever therapy in order to induce remissions. Cases of spontaneous remissions in non-solid tumours have also been re- ported [80] [81] [82]. Nakhla et al. reported on 20 cases of spontaneous regressions in chronic lymphocytic leukaemia (CLL) patients [83]. Del Giudice et al. hypothesise that B-Cell Receptor signaling may play a role in the spontaneous regression of CLL and Hirishanu et al. suggest in their case report that cancer immune surveillance contributed to the spontaneous regression of CLL, in the absence of any other apparent exogenous triggering events [81]. In 2001, Printz

reported on the link between immunological factors and the spontaneous regression of melanomas [84]. Fever, or the fever range of heating, has been cited as a common factor in several spontaneous regression cases [75] [79] [85] [86].

A possible connection between fever and spontaneous regressions is the effects of the heat on the immune system [86] [87] [88] [89]. It may therefore be a possibility that the immune stimulation in the presence of the moderate heat caused by mEHT may contribute to the stabilisation of disease or perhaps even to the spontaneous regression noted in some cases treated only with mEHT.

Although these studies suggest that mEHT may have potential to stabilise disease and manage symptoms, caution must be exercised with regards to pre- scribing, or over-prescribing, mEHT in such cases.
Any potential benefits to the treatments must be carefully balanced against the cost, travelling, the time, and the potential stress on patients with such advanced disease. When appropriately prescribed, mEHT may offer patients and physicians additional treatment options for the palliative management of advanced disease, with minimal risks of adverse events and treatment-related toxicity.

5. Conclusion

Evidence-based statistics are not available for the use of mEHT as a monotherapy. Theory and literature however build an interesting case for the potential benefit of applying mEHT as a monotherapy when standard treatments have failed and when patients have no further options. Determining which cases may benefit from mEHT is an important research question and understanding how mEHT works as a monotherapy may improve the development of protocols for combined therapies. The development of randomised studies on mEHT is needed to confirm these effects and to develop guidelines for the application of mEHT as a monotherapy. Future research on mEHT in a palliative setting could also consider inclusion of immune-modulating agents in the study protocols, in order to enhance the immune-related effects of mEHT.

Acknowledgements

The authors thank the colleagues and mentors who have shared their knowledge on the topic and contributed towards the development of this report.

Conflict of Interests Statement

MS is the medical director of the company that manufactures the mEHT devices: Oncotherm GmBH. The rest of the authors confirm that they do not have any conflicts of interest.

References

[1] Jenson, C. (1904) Experimentelle Untersuchungen über Krebs bei Mäusen. Journal of Cancer Research and Clinical Oncology, 1, 134-138. https://doi.org/10.1007/BF02022613

[2] Loeb, L. (1903) Über Transplantation von Tumoren. Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin, 172, 345-368. https://doi.org/10.1515/9783112371404-013

[3] Selawry, O.S., Goldstein, M.N. and Mccormick, T. (1957) Hyperthermia in Tis- sue-Cultured Cells of Malignant Origin. Cancer Research, 17, 785-791.

[4] Lambert, R.A. (1912) Demonstration of the Greater Susceptibility to Heat of Sar- coma Cells as Compared with Actively Proliferating Connective Tissue Cells. Journal of the American Medical Association, 59, 2147-2148. https://doi.org/10.1001/jama.1912.04270120132016

[5] Dewey, W.C. (2009) Arrhenius Relationships from the Molecule and Cell to the Clinic. International Journal of Hyperthermia, 25, 3-20. https://doi.org/10.1080/02656730902747919

[6] van der Zee, J., Vujaskovic, Z., Kindo, M., et al. (2008) The Kadota Fund International Forum 2004—Clinical Group Consensus. International Journal of Hyperthermia, 24, 111-112. https://doi.org/10.1080/02656730801895058

[7] McNally, N.J. (1991) Book Reviews. The British Journal of Radiology, 64, 565-565. https://doi.org/10.1259/0007-1285-64-762-565-a

[8] Gabriele, P., Orecchia, R., Ragona, R., et al. (1990) Hyperthermia Alone in the Treatment of Recurrences of Malignant Tumors. Cancer, 66, 2191-2195. https://doi.org/10.1002/1097-0142(19901115)66:10<2191::AID-CNCR2820661025> 3.0.CO;2-8

[9] Sannazzari, G.L., Gabriele, P., Orecchia, R., et al. (1989) Results of Hyperthermia, Alone or Combined with Irradiation, in Chest Wall Recurrences of Breast Cancer. Tumori, 75, 284-288. https://doi.org/10.1177/030089168907500320

[10] Warren, S. (1935) Preliminary Study of Effect of Artificial Fever upon Hopeless Tumor Cases. American Journal of Roentgenology, 33, 75.
[11] Storm, F.K., Elliott, R.S., Harrison, W.H., et al. (1981) Radio Frequency Hyperthermia of Advanced Human Sarcomas. Journal of Surgical Oncology, 17, 91-98. https://doi.org/10.1002/jso.2930170202
[12] LeVeen, H.H., Wapnick, S., Piccone, V., et al. (1976) Tumor Eradication by Radio- frequency Therapy: Response in 21 Patients. JAMA, 235, 2198-2200. https://doi.org/10.1001/jama.1976.03260460018014
[13] Marchal, C., Bey, P., Metz, R., et al. (1982) Treatment of Superficial Human Can- cerous Nodules by Local Ultrasound Hyperthermia. British Journal of Cancer, 45, 243-245.
[14] Kok, H.P., Wust, P., Stauffer, P.R., et al. (2015) Current State of the Art of Regional Hyperthermia Treatment Planning: A Review. Radiation Oncology, 10, 503. https://doi.org/10.1186/s13014-015-0503-8
[15] Dewhirst, M.W., Vujaskovic, Z., Jones, E., et al. (2005) Re-Setting the Biologic Rationale for Thermal Therapy. International Journal of Hyperthermia, 21, 779-790. https://doi.org/10.1080/02656730500271668
[16] Walker, A., McCallum, H.M., Wheldon, T.E., et al. (1978) Promotion of Metastasis of C3H Mouse Mammary Carcinoma by Local Hyperthermia. British Journal of Cancer, 38, 561-563. https://doi.org/10.1038/bjc.1978.246
[17] Dickson, J.A. and Ellis, H.A. (1976) The Influence of Tumor Volume and the Degree of Heating on the Response of the Solid Yoshida Sarcoma to Hyperthermia (40˚ - 42˚). Cancer Research, 36, 1188-1195.
[18] Datta, N.R., Ordóñez, S.G., Gaipl, U.S., et al. (2015) Local Hyperthermia Combined with Radiotherapy and/or Chemotherapy: Recent Advances and Promises for the Future. Cancer Treatment Reviews, 41, 742-753. https://doi.org/10.1016/j.ctrv.2015.05.009
[19] Mallory, M., Gogineni, E., Jones, G.C., et al. (2016) Therapeutic Hyperthermia: The Old, the New, and the Upcoming. Critical Reviews in Oncology/Hematology, 97, 56-64. https://doi.org/10.1016/j.critrevonc.2015.08.003
[20] Hahn, E.W., Alfieri, A.A. and Kim, J.H. (1978) The Significance of Local Tumor Hyperthermia/Radiation on the Production of Disseminated Disease. Radiation Oncology, 4, 141-142. https://doi.org/10.1016/0360-3016(78)90321-8
[21] Ando, K., Urazno, M., Kenton, L., et al. (1987) Effect of Thermochemotherapy on the Development of Spontaneous Lung Metastases. International Journal of Hyperthermia, 3, 453-458. https://doi.org/10.3109/02656738709140415
[22] Emami, B., Scott, C., Perez, C.A., et al. (1996) Phase III Study of Interstitial Thermoradiotherapy Compared with Interstitial Radiotherapy Alone in the Treatment of Recurrent or Persistent Human Tumors: A Prospectively Controlled Randomized Study by the Radiation Therapy Oncology Group. International Journal of Radiation Oncology, Biology, Physics, 34, 1097-1104. https://doi.org/10.1016/0360-3016(95)02137-X
[23] Jones, E.L., Oleson, J.R., Prosnitz, L.R., et al. (2005) Randomized Trial of Hype thermia and Radiation for Superficial Tumors. Journal of Clinical Oncology, 23, 3079-3085. https://doi.org/10.1200/JCO.2005.05.520
[24] Harima, Y., Ohguri, T., Imada, H., et al. (2016) A Multicentre Randomised Clinical Trial of Chemoradiotherapy plus Hyperthermia versus Chemoradiotherapy Alone in Patients with Locally Advanced Cervical Cancer. International Journal of Hyperthermia, 32, 801-808. https://doi.org/10.1080/02656736.2016.1213430
[25] Vernon, C., Hand, J., Field, S., et al. (1996) Radiotherapy with or without Hyperthermia for Superficial Breast. International Journal of Radiation Oncology, Biology, Physics, 35, 731-744. https://doi.org/10.1016/0360-3016(96)00154-X
[26] De Bruijne, M., Holt, B. Van Der, Van Rhoon, G.C., et al. (2010) Evaluation of CEM43° CT90 Thermal Dose in Superficial Hyperthermia: A Retrospective Analysis. Strahlentherapie und Onkologie, 186, 436-443. https://doi.org/10.1007/s00066-010-2146-x
[27] Fatehi, D., Van der Zee, J., Van der Wal, E., et al. (2006) Temperature Data Analysis for 22 Patients with Advanced Cervical Carcinoma Treated in Rotterdam Using Radiotherapy, Hyperthermia and Chemotherapy: A Reference Point Is Needed. Inter- national Journal of Hyperthermia, 22, 353-363. https://doi.org/10.1080/02656730600715796
[28] Pandita, T.K., Pandita, S. and Bhaumik, S.R. (2009) Molecular Parameters of Hyperthermia for Radiosensitization. Critical Reviews™ in Eukaryotic Gene Expression, 19, 235-251. https://doi.org/10.1615/CritRevEukarGeneExpr.v19.i3.50
[29] Oei, A.L., Vriend, L.E.M., Crezee, J., Franken, N.A.P. and Krawczyk, P.M. (2015) Effects of Hyperthermia on DNA Repair Pathways: One Treatment to Inhibit Them All. Radiation Oncology, 10, 165. https://doi.org/10.1186/s13014-015-0462-0

[30] Lepock, J.R. (2004) Role of Nuclear Protein Denaturation and Aggregation in Thermal Radiosensitization. International Journal of Hyperthermia, 20, 115-130. https://doi.org/10.1080/02656730310001637334
[31] Kampinga, H.H. and Dikomey, E. (2001) Hyperthermic Radio-Sensitization: Mode of Action and Clinical Relevance. International Journal of Radiation Biology, 77, 399-408. https://doi.org/10.1080/09553000010024687
[32] Roti Roti, J.L. (2008) Cellular Responses to Hyperthermia (40-46 Degrees C): Cell Killing and Molecular Events. International Journal of Hyperthermia, 24, 3-15. https://doi.org/10.1080/02656730701769841
[33] Griffin, R.J., Dings, R.P.M., Jamshidi-Parsian, A. and Song, C.W. (2010) Mild Temperature Hyperthermia and Radiation Therapy: Role of Tumour Vascular Thermotolerance and Relevant Physiological Factors. International Journal of Hyperthermia, 26, 256-263. https://doi.org/10.3109/02656730903453546
[34] Peeken, J.C., Vaupel, P., Combs, S.E. and Combs, S.E. (2017) Integrating Hyperthermia into Modern Radiation Oncology: What Evidence Is Necessary? Frontiers in Oncology, 7, Article No. 132. https://doi.org/10.3389/fonc.2017.00132
[35] Werthmöller, N., Frey, B., Rückert, M., Lotter, M., Fietkau, R. and Gaipl, U.S. (2016) Combination of Ionising Radiation with Hyperthermia Increases the Immunogenic Potential of B16-F10 Melanoma Cells in Vitro and in Vivo. International Journal of Hyperthermia, 32, 23-30. https://doi.org/10.3109/02656736.2015.1106011
[36] Frey, B., Rückert, M., Deloch, L., Rühle, P.F., Derer, A., Fietkau, R. and Gaipl, U.S. (2017) Immunomodulation by Ionizing Radiation—Impact for Design of Radio-Immunotherapies and for Treatment of Inflammatory Diseases. Immunological Reviews, 280, 231-248. https://doi.org/10.1111/imr.12572
[37] Schmitt, E., Gehrmann, M., Brunet, M., Multhoff, G. and Garrido, C. (2007) Intra- cellular and Extracellular Functions of Heat Shock Proteins: Repercussions in Can- cer Therapy. Journal of Leukocyte Biology, 81, 15-27. https://doi.org/10.1189/jlb.0306167
[38] van der Zee, J. (2002) Heating the Patient: A Promising Approach? Annals of Oncology, 13, 1173-1184. https://doi.org/10.1093/annonc/mdf280
[39] Szasz, A., Szasz, O. and Szasz, N. (2001) Electro-Hyperthermia: A New Paradigm in Cancer Therapy. Deutsche Zeitschrift für Onkologie, 33, 91-99. https://doi.org/10.1055/s-2001-19447
[40] Fiorentini, G. and Szasz, A. (2006) Hyperthermia Today: Electric Energy, a New Opportunity in Cancer Treatment. Journal of Cancer Research and Therapeutics, 2, 41-46. https://doi.org/10.4103/0973-1482.25848
[41] Mohamed, F., Marchettini, P., Stuart, O.A., Urano, M. and Sugarbaker, P.H. (2003) Thermal Enhancement of New Chemotherapeutic Agents at Moderate Hyperthermia. Annals of Surgical Oncology, 10, 463-468. https://doi.org/10.1245/ASO.2003.08.006
[42] Lee, S.-Y., Kim, J.-H., Han, Y.-H., et al. (2018) The Effect of Modulated Electro-Hyperthermia on Temperature and Blood Flow in Human Cervical Carcinoma. International Journal of Hyperthermia, 34, 953-960. https://doi.org/10.1080/02656736.2018.1423709
[43] Minnaar, C.A., Kotzen, J.A., Ayeni, O.A., et al. (2019) The Effect of Modulated Electro-Hyperthermia on Local Disease Control in HIV-Positive and -Negative Cervical Cancer Women in South Africa: Early Results from a Phase III Randomised Controlled Trial. PLOS ONE, 14, e0217894. https://doi.org/10.1371/journal.pone.0217894
[44] Minnaar, C.A., Kotzen, J.A., Naidoo, T., et al. (2020) Analysis of the Effects of mEHT on the Treatment-Related Toxicity and Quality of Life of HIV-Positive Cervical Cancer Patients. International Journal of Hyperthermia, 37, 263-272. https://doi.org/10.1080/02656736.2020.1737253
[45] Andocs, G., Renner, H., Balogh, L., et al. (2009) Strong Synergy of Heat and Modulated Electromagnetic Field in Tumor Cell Killing. Strahlentherapie und Onkologie, 185, 120-126. https://doi.org/10.1007/s00066-009-1903-1
[46] Yang, K.L., Huang, C.C., Chi, M.S., et al. (2016) In Vitro Comparison of Conventional Hyperthermia and Modulated Electro-Hyperthermia. Oncotarget, 7, 84082- 84092. https://doi.org/10.18632/oncotarget.11444
[47] Tsang, Y.W., Huang, C.C., Yang, K.L., et al. (2015) Improving Immunological Tu- mor Microenvironment Using Electro-Hyperthermia Followed by Dendritic Cell Immunotherapy. BMC Cancer, 15, Article No. 708. https://doi.org/10.1186/s12885-015-1690-2
[48] Qin, W., Akutsu, Y., Andocs, G., et al. (2014) Modulated Electro-Hyperthermia Enhances Dendritic Cell Therapy through an Abscopal Effect in Mice. Oncology Reports, 32, 2373-2379. https://doi.org/10.3892/or.2014.3500
[49] Andocs, G., Meggyeshazi, N., Balogh, L., et al. (2015) Upregulation of Heat Shock Proteins and the Promotion of Damage-Associated Molecular Pattern Signals in a Colorectal Cancer Model by

Modulated Electrohyperthermia. Cell Stress and Chaperones, 20, 37-46. https://doi.org/10.1007/s12192-014-0523-6

[50] Meggyeshazi, N., Gabor, A., Spisak, S., et al. (2013) Early Changes in mRNA and Protein Expression Related to Cancer Treatment by Modulated Electrohyperthermia. Conference Papers in Medicine, 2013, Article ID: 249563. https://doi.org/10.1155/2013/249563

[51] Cha, J., Jeon, T.W., Lee, C.G., et al. (2015) Electro-Hyperthermia Inhibits Glioma Tumorigenicity through the Induction of E2F1-Mediated Apoptosis. International Journal of Hyperthermia, 31, 784-792. https://doi.org/10.3109/02656736.2015.1069411

[52] Jeon, T.W., Yang, H., Lee, C.G., et al. (2016) Electro-Hyperthermia Up-Regulates Tumour Suppressor Septin 4 to Induce Apoptotic Cell Death in Hepatocellular Carcinoma. International Journal of Hyperthermia, 32, 648-656. https://doi.org/10.1080/02656736.2016.1186290

[53] Jeung, T.S., Ma, S.Y., Yu, J., et al. (2013) Cases That Respond to Oncothermia Monotherapy. Conference Papers in Medicine, 2013, Article ID: 392480. https://doi.org/10.1155/2013/392480

[54] Lindegaard, J.C. (1992) Winner of the Lund Science Award 1992 Thermosensitization Induced by Step-Down Heating: A Review on Heat-Induced Sensitization to Hyperthermia Alone or Hyperthermia Combined with Radiation. International Journal of Hyperthermia, 8, 561-586. https://doi.org/10.3109/02656739209037994

[55] Lindegaard, J.C. and Overgaard, J. (1988) Effect of Step-Down Heating on Hyper- thermic Radiosensitization in an Experimental Tumor and a Normal Tissue in Vi- vo. Journal of Radiotherapy and Oncology, 11, 143-151. https://doi.org/10.1016/0167-8140(88)90250-2

[56] Szigeti, G.P., Szasz, O. and Hegyi, G. (2016) Personalised Dosing of Hyperthermia. Journal of Cancer Diagnosis, 1, 107. https://doi.org/10.4172/2476-2253.1000107

[57] Hall, E.J. and Roizintowle, L. (2013) Biological Effects of Heat. Cancer Research, 44, 4708-4713.

[58] Rybinski, M., Szymanska, Z., Lasota, S., et al. (2013) Modelling the Efficacy of Hyperthermia Treatment. Journal of the Royal Society Interface, 10, Article ID: 20130527. https://doi.org/10.1098/rsif.2013.0527

[59] Hegyi, G., Szigeti, G.P. and Szász, A. (2013) Hyperthermia versus Oncothermia: Cellular Effects in Complementary Cancer Therapy. Evidence-Based Complementary and Alternative Medicine, 2013, Article ID: 672873. https://doi.org/10.1155/2013/672873

[60] Hager, E., Dziambor, H., Hohmann, D., et al. (1999) Deep Hyperthermia with Radiofrequencies in Patients with Liver Metastases from Colorectal Cancer. Anticancer Research, 19, 3403-3408.

[61] Ferrari, V.D., De Ponti, S., Valcamonico, F., et al. (2007) Deep Electro-Hyperthermia (EHY) with or without Thermo-Active Agents in Patients with Advanced Hepatic Cell Carcinoma: Phase II Study. Journal of Clinical Oncology, 25, Article No. 15168. https://doi.org/10.1200/jco.2007.25.18_suppl.15168

[62] Fiorentini, G., Giovanis, P., Rossi, S., et al. (2006) A Phase II Clinical Study on Re- lapsed Malignant Gliomas Treated with Electro-Hyperthermia. In Vivo, 20, 721-724.

[63] Fiorentini, G., Sarti, D., Milandri, C., et al. (2019) Modulated Electrohyperthermia in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: Retrospective Multicenter Controlled Study. Integrative Cancer Therapies, Epub 2018. https://doi.org/10.1177/1534735418812691

[64] Fiorentini, G., Sarti, D., Casadei, V., et al. (2019) Modulated Electro-Hyperthermia as Palliative Treatment for Pancreatic Cancer: A Retrospective Observational Study on 106 Patients. Integrative Cancer Therapies, Epub 2019. https://doi.org/10.1177/1534735419878505

[65] Minakuchi, H., Hirayama, R., Sawai, S., et al. (1990) Clinical Trials of Long-Term RF Local Hyperthermia for Advanced Gastric Cancer. The Japanese Journal of Surgery, 20, 238-239. https://doi.org/10.1007/BF02470777

[66] Lee, S.Y., Lee, N.R., Cho, D., et al. (2017) Treatment Outcome Analysis of Chemotherapy Combined with Modulated Electro-Hyperthermia Compared with Chemo- therapy Alone for Recurrent Cervical Cancer, Following Irradiation. Oncology Letters, 14, 73-78. https://doi.org/10.3892/ol.2017.6117

[67] Gadaleta-Caldarola, G., Infusino, S., Galise, I., et al. (2014) Sorafenib and Locoregional Deep Electro-Hyperthermia in Advanced Hepatocellular Carcinoma: A Phase II Study. Oncology Letters, 8, 1783-1787. https://doi.org/10.3892/ol.2014.2376

[68] Yoo, H.J., Lim, M.C., Seo, S.S., et al. (2019) Phase I/II Clinical Trial of Modulated Electro-Hyperthermia Treatment in Patients with Relapsed, Refractory or Progressive Heavily Treated Ovarian Cancer. Japanese Journal of Clinical Oncology, 49, 832-838. https://doi.org/10.1093/jjco/hyz071

[69] Andocs, G., Rehman, M.U., Zhao. Q-L., et al. (2016) Comparison of Biological Effects of Modulated Electro-Hyperthermia and Conventional Heat Treatment in Human Lymphoma U937 Cells. Cell Death Discovery, 2, 16039. https://doi.org/10.1038/cddiscovery.2016.39

[70] Meggyeshazi, N., Andocs, G., Balogh, L., et al. (2014) DNA Fragmentation and Caspase-Independent Programmed Cell Death by Modulated Electrohyperthermia. Strahlentherapie und Onkologie, 190, 815-822. https://doi.org/10.1007/s00066-014-0617-1

[71] Vancsik, T., Kovago, C., Kiss, E., et al. (2018) Modulated Electro-Hyperthermia Induced Loco-Regional and Systemic Tumor Destruction in Colorectal Cancer Allo- grafts. Journal of Cancer, 9, 41-53. https://doi.org/10.7150/jca.21520
[72] Papp, E., Vancsik, T., Kiss, E., et al. (2017) Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (mEHT). Open Journal of Biophysics, 7, 216-229. https://doi.org/10.4236/ojbiphy.2017.74016
[73] Minnaar, C.A., Kotzen, J.A., Ayeni, O.A., et al. (2020) Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients. Frontiers in Oncology, 10, Article No. 376. https://doi.org/10.3389/fonc.2020.00376
[74] Minnaar, C.A., Maposa, I., Kotzen, J.A., et al. (2022) Effects of Modulated Elec- tro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients. Cancers, 14, 656. https://doi.org/10.3390/cancers14030656
[75] Kumar, T., Patel, N. and Talwar, A. (2010) Spontaneous Regression of Thoracic Malignancies. Respiratory Medicine, 104, 1543-1550. https://doi.org/10.1016/j.rmed.2010.04.026
[76] Herwig-Carl, M.C. and Loeffler, K.U. (2020) Regression of Periocular Basal Cell Carcinoma: A Report of Four Cases with Clinicopathologic Correlation. Ocular Oncology and Pathology, 6, 107-114. https://doi.org/10.1159/000501370
[77] Liu, J., Wu, X.W., Hao, X.W., et al. (2020) Spontaneous Regression of Stage III Neuroblastoma: A Case Report. World Journal of Clinical Cases, 8, 436-443. https://doi.org/10.12998/wjcc.v8.i2.436
[78] Challis, G.B. and Stam, H.J. (1990) The Spontaneous Regression of Cancer: A Re- view of Cases from 1900 to 1987. Acta Oncologica, 29, 545-550. https://doi.org/10.3109/02841869009090048
[79] Hobohm, U. (2001) Fever and Cancer in Perspective. Cancer Immunology, Immunotherapy, 50, 391-396. https://doi.org/10.1007/s002620100216
[80] Khanal, N., Bhatt, V.R. and Armitage, J.O. (2015) Spontaneous Regression of Chronic Lymphocytic Leukemia. Journal of Case Reports in Practice, 3, 67-70.
[81] Herishanu, Y., Solar, I., Ben-Ezra, J., et al. (2013) Complete Spontaneous Regression of Chronic Lymphocytic Leukemia. Journal of Clinical Oncology, 31, 2014-2016.
[82] Thomas, R., Ribeiro, I., Shepherd, P., et al. (2002) Spontaneous Clinical Regression in Chronic Lymphocytic Leukaemia. British Journal of Haematology, 116, 341-345. https://doi.org/10.1046/j.1365-2141.2002.03286.x
[83] Nakhla, P.S., Butera, J.N., Treaba, D.O., et al. (2013) Spontaneous Regression of Chronic Lymphocytic Leukemia to a Monoclonal B-Lymphocytosis or to a Normal Phenotype. Leukemia & Lymphoma, 54, 1647-1651. https://doi.org/10.3109/10428194.2012.753449
[84] Printz, C. (2001) Spontaneous Regression of Melanoma May Offer Insight into Cancer Immunology. JNCI: Journal of the National Cancer Institute, 93, 1047-1048. https://doi.org/10.1093/jnci/93.14.1047
[85] Hobohm, U., Stanford, J.L. and Grange, J.M. (2008) Pathogen-Associated Molecular Pattern in Cancer Immunotherapy. Critical ReviewsTM in Immunology, 28, 95-107. https://doi.org/10.1615/CritRevImmunol.v28.i2.10
[86] Thomas, J.A. and Badini, M. (2011) The Role of Innate Immunity in Spontaneous Regression of Cancer. Indian Journal of Cancer, 48, 246-251. https://doi.org/10.4103/0019-509X.82887
[87] Ricci, S.B. and Cerchiari, U. (2010) Spontaneous Regression of Malignant Tumors: Importance of the Immune System and Other Factors (Review). Oncology Letters, 1, 941-945. https://doi.org/10.3892/ol.2010.176
[88] Jessy, T. (2011) Immunity over Inability: The Spontaneous Regression of Cancer. Journal of Natural Science, Biology and Medicine, 2, 43-49. https://doi.org/10.4103/0976-9668.82318
[89] Overwijk, W.W., Theoret, M.R., Finkelstein, S.E., et al. (2003) Tumor Regression and Autoimmunity after Reversal of a Functionally Tolerant State of Self-Reactive CD8+ T Cells. Journal of Experimental Medicine, 198, 569-580. https://doi.org/10.1084/jem.20030590

Supportive and Palliative Care in Cancer Therapies - Path from Tumor-Driven Therapies to Patient-Driven Ones

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Cite this article as:
Minnaar, C.A. et al. (2022): Supportive and Palliative Care in Cancer Therapies - Path from Tumor-Driven Therapies to Patient-Driven Ones. International Journal of Clinical Medicine, 13, 287-359.
https://doi.org/10.4236/ijcm.2022.137024

Oncothermia Journal 32, September 2022: 106 – 154,
http://www.oncotherm.com/sites/oncotherm/files/2022-09/Minnaar_Supportive_and_Palliative.pdf

Abstract:

Cancer patients frequently report a set of symptoms including fatigue, pain, and physiological and social distress. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices. Medical professionals have a responsibility to clear this field and concentrate on patients' well-being and personal needs. According to our approach, the integration of supportive and palliative care with conventional therapies needs a change of paradigm from tumour-driven to patient-driven treatment actions. Supportive/palliative care includes a broad spectrum of applied methods, including medications, nourishments, electrical effects, and psycho and social supports. Our goal is to discuss the possibilities for combining conventional oncotherapies with additional supportive/palliative care and to give suggestions on a professional basis.

Keywords:

Cancer, Vitamins, Minerals, Fungi, Immune, Phytomedicine, Complexity, Electric-Stimuli, Hyperthermia, mEHT

1. Background

Cancer patients frequently report a complex syndrome of the disease, a set of symptoms including fatigue, pain, and physiological and social distresses. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices.
The application of supportive and supplemental drugs for cancer patients is a hot topic not only in the relevant professional literature, but also in patients' self-help groups and traditionally formed societies, and among patients' family members who would like to help their ill relatives. Supportive care (SC) is a general category of attention regarding the patient throughout the complete course of cancer treatment, involving self-help support, information exchange, physio- logical and psychological support, symptom control, social support, rehabilitation, complementary therapies, spiritual support, palliative care, and end-of-life care too [1]. SC could be provided at all stages and on all pathways of cancer treatment from the established diagnosis and therapy process onward. SC is a necessary condition for accurate cancer treatment, and, of course, SC is very personalized. Due to the absence of a standard protocol of SC it has a risk of non-reproducibility, so even the best supportive care (BSC) cannot be simply adopted as a reference for any clinical trial [2]. SC is focused on the well-being of the patient, improving the quality of life (QoL) and decreasing adverse effects of ongoing treatments or preparing conditions for planned therapy.

The growing incidence of malignancies drives the cancer therapy market. Cooperation in academic research, mergers in the pharmaceutical industry, and the gradual harmonization of the activities of various organizations make the field of supportive therapies massively influential in the global market [3]. An estimated 16.9 million cancer survivors were registered in the United States on the 1st of January 2019 [4]. Due to increasing survival rates a huge number, 22.1 million patients, are estimated for the 1st of January 2030 [4]. Two thirds of cancer survivors (67%) have 5+ years of overall survival, and 18% were diagnosed 20+ years ago, and also nearly 2/3 of cancer patients are 65+ years old [4], so the demand for SC is massively growing with these numbers. Consequently, many uncontrolled patient's practices of SC (pSC) grow rapidly, supported by massive advertising and "mouth propaganda".

The hopes and beliefs in traditional healing practices and pSC are supported by information reported about various spontaneous regressions. As early as the beginning of the last century, 185 spontaneous regressions were collected [5] and another collection of cases was published in the early 1960s: 202 cases were collected within four years [6], while 98 cases were also shown in the middle of that decade [7]. Many surprising spontaneous remissions were described in a mono- graph [8]. The literature on the spontaneous remission of cancer is impressive [9] [10] [11] [12]. A large number of clinical cases have been collected to study the topic: 176 cases between 1900 and 1960 [13] [14]; 489 cases described from 1900 to 1987 [15], and a large meta-analysis was applied to about 1000 cases [16]. The topic was brought into focus again a few years ago by the "Armstrong effect" [17]. These published data give special (sometimes illusionary) hope to cancer patients and also to professionals. However, statistical evaluation is not possible on the sporadic facts, and pieces of weak evidence may give false hopes, supporting the belief that the patient often self-heals with the help of unprofessional healers.

The main realistic expectation of SC is the improving of the QoL, and by this progress the establishing of a condition of well-tolerated and elongated overall survival time too. Health professionals must pay more attention to patients' fear and complaints during therapy. Professionals have to offer appropriate SC, explaining the disadvantages of the uncontrolled intake of drugs in pSC, and clarifying the possible advantages of the regulation of diet and supplements by experts.

Nevertheless, the uncontrolled pSC became common in the self-care of cancer sufferers. Statistics show that a vast number of cancer patients use various herbal products without questioning the physician or nurse in connection with conventional cancer therapies [18]. Unfortunately, many of these intakes of additional drugs are not reported to the oncologist, though their interactions with chemo- therapy could limit the benefit of the full therapy. The numbers are high: 81.7% of patients use herbs uncontrolledly during the various chemotherapies, and 94.3% of patients take herbs/vitamins before their surgery. The influence to use herbs intended to help with complaints concerning the conventional therapies came 39.8% from the media and 20% from internet searches, the patients' own physicians recommending of the applications in only about 1% of cases [16]. The results of another survey [19] also showed that patients having chemotherapy frequently use pSCs believing in their advantages. Some supplements are harmless, but many have interactions with the actual conventional therapy and could have significant disadvantages too. Almost one third (28%) of the patients were at risk due to the harmful interactions of pSC intake with the chemotherapy they received [20]. The vast use of pSC is based on various hopes and beliefs. The use of supplementary herbs or vitamins is rarely documented; frequently patients rely on their friends and naturopathic providers who are many times not in complete knowledge about the actual status of the patient his/her basic therapy. Despite the weak documentation and the small number of pieces of evidence, patients and their families massively request pSC, creating a not negligible demand for the doctors. This "grey zone" of treatment has to be investigated and a definite evidence-based approach established to put pSC in its place among the cancer therapies.

The patients in this way become easy targets of the misconceptions of unprofessional laypersons or, in more serious cases, they become the victims of quackeries, fake information, and harmful cheats.

Frequently the leading causes of imbalance in patient's decision-making are:

- a massive fear of the side-effects of conventional therapies;
- suffering from declining quality of life;
- the vast number of irresponsible advertisings by various information re- sources in society, including via modern information technology.

The high-level demand for supportive care of cancer patients in physiological and psychological help and in getting information about appropriate changes to make to their lifestyle is massively under-satisfied [21] [22]. The absence of an appropriate understanding of supportive care for cancer patients results in its underutilization in medical applications. The non-appropriate pSC accompanied with a lack of knowledge among healthcare professionals. Consequently, the sometimes inappropriate evaluations of physicians significantly limit the development of the cancer-supporting therapeutic industry and sometimes push disoriented patients to unproven, uncontrolled courses of treatment. Another unrecognized and uncontrolled source of herbs and supplemental drugs are the local historical diets and traditional habits which may interact with drugs [23]. The disease and its therapy may drive patients to seek a change to their regular every-day lifestyle, including a change to their traditional diet, which could be culturally inherited according to national character or individual family lore. Psychosocial distress could be an additional factor in the lifestyle change of the patient [24]. Due to this complexity, SC varies by country due to cultural differences and available resources [25]. The change in diet could involve not only an alteration to the set of nutrients consumed but in fact a complete rearrangement of the usual daily life of the patient, forming a new lifestyle and preferences.

The need for effective supportive cancer care increases with the longer survival times and with the transformation of previously fatal cancers to chronic dis- ease [26]. The further development of the field requires a reliable and valid evaluation of global needs for supportive care with standardized guidelines [27], which could differ according to specific challenges in various countries [28].

The increase in the number of patients affected by various anti-cancer therapies, or by those therapies having become ineffective, pumps-up the global market for palliative and supportive care, which is a clear market for home-care too [29]. pSC is a special and considerable part of the SC market, pumping up the need for herbs, supplementary drugs, and vitamins by mass marketing and the extreme attention of social media. The time is ripe for a change of paradigm.

The meaning of SC by clinicians drastically narrows in everyday patient practices, becoming limited to the simple addition of dietary supplements, di- et-protocols, herbs, vitamins, teas, decoctions, and other "home-made" practices, without the assistance of medical professionals. Proper SC is based on cooperation between the patient and the doctor, the therapist, who knows well the applied protocol, the possible adverse effects, and the actual support needs. The objective of our article shows for professionals the complexity and great potential in the SC.

2. Change of Paradigm

The patient demands for SC met with the medical needs of the broad range completing the curative therapies. A high number of patients strongly request such complementary pSC services despite these mostly having mere shreds of evidence. The Guideline of the National Health Service (NHS, UK) [1] focuses on the needs of patients, expressing the importance of providing reliable information for proper decision-making, and taking care that patients can access these therapies safely when they insist on a therapy. Interestingly, end-of-life care does not increase the survival when the therapy directly includes the patients (or "the family members") preferences [30].

SC has to consider the complexity of cancer and its embedded value in the family and society. However, its proper application needs a change of paradigm from cancer-driven to patient-driven therapy. This refocused attention becomes strong only when the conventional cancer-driven approach is limited or has failed, and then palliative treatment (PT) will be at the centre of considerations, with concentration on the QoL and the easing of the suffering of the patient. The PT is this phase the only help, and in the meaning of the patient support this phase is an intensive and medically controlled SC. Unfortunately, PT has no unified definition [31], but the common meaning generally reached is that it does not follow a curative approach but concentrates on the elimination of symptoms. It is the active holistic care of patients with advanced, progressive illness, managing the pain and other symptoms, predominating in end-of-life care [32]. More detailed definitions have been elaborated by the NHS (UK) [1], listing the needs for SC and PT for medical professionals. The key idea of SC is not a distinct specialty but is the responsibility of all health and social care professionals delivering care. It requires a spectrum of skills, extending from basic skills to highly specific expertise and experience. PT is described thus [31]: "Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families". The importance of SC/PT is widely recognized and is provided not only by medical experts, but the family, the social environment, and other care-providers have a part in the com- plex process.

The WHO defines PT more widely [33]: "Palliative care is an approach that improves the quality of life of patients and their families facing the problems as- sociated with life-threatening illness and is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life."

Despite the above definitions, some confusions between palliative and supportive care exist in medical practice. The main attempts to distinguish SC from PT point to apparent contradictions between them, listing that PT is passive care, is relatively cheap, and is applied for a short time during the end-of-life care; while SC is an active intervention, chronical, and expensive [34]. In this approach, it looks as if SC and PT are complementary, but in the complex patient-oriented therapy these are not distinguishable into disjunct groups, so we cannot formulate these independently from each other. In general however, supportive care is rather oriented towards helping the patient to achieve remission as long as it is feasible by the "holistic" combination of therapeutic and supportive interventions.

2.1. Challenging Present Conventional Consensus

The actual challenge of SC/PT is the inherent complexity of the human being and in consequence the complexity of human medicine. The rigid conventional consensus in oncology, which is oriented towards the tumour, somehow forgot that the lesion belongs to an individual patient. This conceptualisation has led to overly simplistic therapeutic protocols. There is a slogan sometimes quoted by doctors to patients who are suffering from the side effects of the actual medication: "The drug which has no side effect has no effect either". This opinion mirrors the missing complexity of the therapy; the drug which is administered focuses on one effect, ignoring its embedded interconnections to the complex system. SC/PT has to complete the therapy, compensating for the missing apprehension of complexity in the approach of the primary treatment.

SC and PT focus on the patient, who is the host of the malignancy, while oncology concentrates on the tumorous lesion, ignoring the complexity of the dis- ease. The missing complexity has to be found again, answering the question as to "where medicine went wrong" [35]. The medical paradigm of oncology has to focus on the complexity of the malignant situation and evaluate and treat the patient as a whole.

The aim of this article is to summarize the recent achievements of pSC applicable in the PT process and to firmly embed the importance of general SC in everyday oncological practice. We want to point to the responsibility of those health professionals showing the optimal way to use pSC, giving stable support for disoriented patients, preventing them from becoming victims of quackeries or simply of their own beliefs.

The SC of individuals could start with the prevention of malignant diseases by advising on lifestyle and diet, as well as by proposals for checks depending on the individual's various life-conditions, habits, and environmental circumstances, including the actual daily risk factors and the ages of the subjects. In diagnosed, established malignant disease, supportive care focuses on the treatment of cancer-related diseases, comorbidities, and side effects of the active therapy [36]. Palliative care usually follows supportive care, when the support is not enough, and in many cases when the active curative approach has failed [37]. The goal of both is to keep the QoL as high as possible. This is the final turning point from the tumour-oriented to the patient-oriented concept. We have to have a certain change of paradigm. Interestingly, artificial intelligence and robotic technologies started to enter this field too [38].

To meet patients' demands, there are three major categories of pSC to be ap- plied in the frame of the general SC:

1) Increase the efficacy of conventional cancer therapies, maximizing their curative effect.
2) Decrease the adverse effects of conventional therapies, increasing the quality of life of the patient.
3) Regarding the newest developments of immuno-oncology, the support of the immune system, and the revitalizing of the toxic degradation of immune effects is a new goal.

All of these categories are focused on the patient-guided treatment plan in- stead of the tumour-guided methodology (Figure 1). The curative effect must consider the patient's personality and individual factors (like comorbidities, allergies, disease history, environmental factors, dietary factors, life-style). Local treatment has to be effective systemically too.

Anyway, the change from tumour-focused to patient-focused therapies is inherently included in the definition of malignancy. Cancer is a systemic disease from its early beginnings in the body. By the conventional view the PT period of the treatment starts only in advanced cases, when the metastases limit curative interventions. Patients suffering extensively by the intensified illness need ex- tended support. Hope and sometimes false advertisements and unprofessional bits of "helpful" advice make the patient vulnerable and could orient the patient towards uncontrolled pSC and PT. It is the task of healthcare professionals to keep the patient on a safe course of treatment together with providing patient satisfaction. The satisfactory condition is mostly related to the QoL and, of course, the elongation of the life-span with acceptable living conditions.

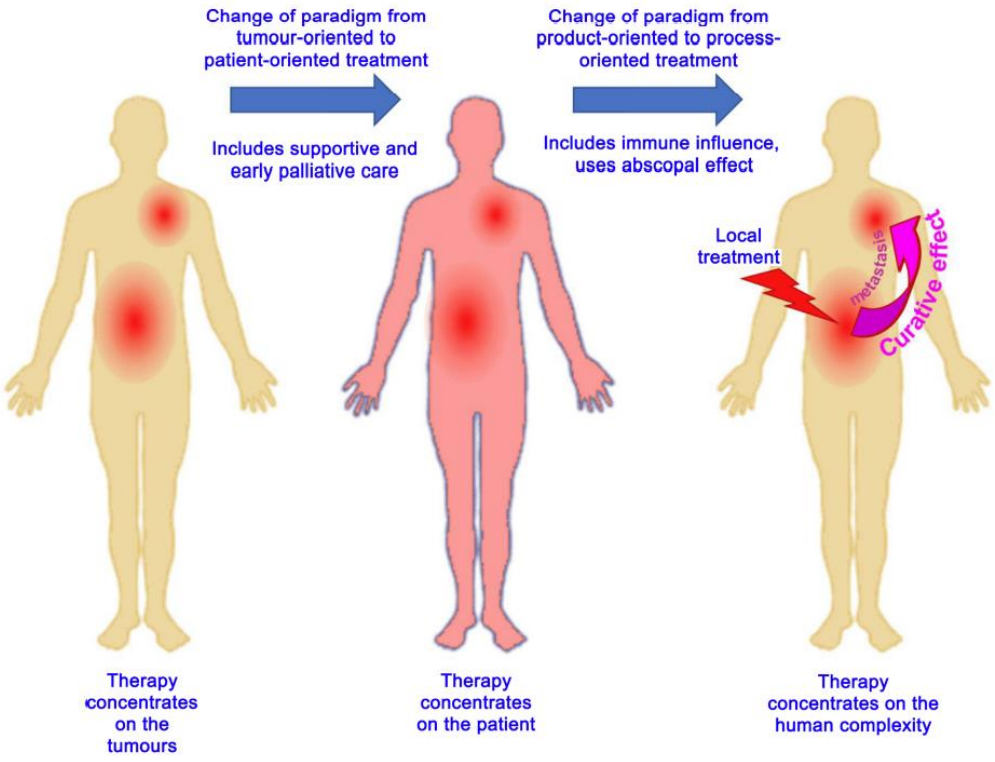


Figure 1. It is time to change the paradigm of cancer therapies, and take the patient as whole in the centre of actions.

The patient-oriented attitude of the therapy concept re-establishes the complexity in the mind of therapist and offers for the patient the possibility of a better prognosis, longer survival, and higher quality of life. The integration of SC/PT into oncology relies on specific knowledge and skills [32]. The two existing models of SC and PT have to be integrated, challenging a certain "dualistic perspective" [32]. The classical cancer treatments are tumour-oriented, focusing their attention on eliminating the malignant tissues. These intensive processes can cause extensive side effects and may cause irreversible comorbidities too. The growing number of serious adverse effects and the lack of effective approaches to managing them raises new challenges [39]. Such new, high-hope treatments as targeted therapies have serious side effects [40] and can decrease the QoL of the patient [41]. Immunotherapy may even worsen cancer development, causing hyper-progression [42], well showing a double-edged sword effect of immuno-therapeutics in cancer treatment [43].

The conventional therapies, led by chemo and hormonal remedies, have lost their overall primacy. According to a WHO consultation publication [44], the classical chemo and hormonal therapies can be grouped into five categories by their effectiveness: 1) potentially curative, 2) adjuvant with benefit for local dis- ease, 3) palliative in metastatic stages, 4) local control enhanced, and 5) chemo- therapy is ineffective. The ten most frequent cancers (lung, stomach, breast, colorectal, cervix, head and neck, lymphoma, hepatobiliary, oesophagus, and prostate) are all in category 3, which well supports the importance of the PT processes. Most of the essential high priority drugs are developed for the top ten cancers [44], and despite the mostly improving overall survivals, the results are not satisfactory yet. It is obvious that in most of the disease manifestations PT/SC is not an alternative treatment to the curative conventional chemotherapies but it is a part of the therapy.

Expectations of a simple situation in a system which has multiple regulatory feedbacks and interactions which request a harmonic coexistence of the regulatory actions is unrealistic. Chronic inflammation often promotes tumour development, including the dissemination and formation of metastases too. Acute inflammation, however, could act oppositely, causing a dilemma [45]. The ac- companying pain, depression, psychosocial stress, fatigue, and other bad conditions of patients combine to accelerate their loss of QoL and shorten their survival. It could be a matter of slowing the acceleration of symptoms when PT/SC care starts at the first diagnosis of a fatal malignancy [46]. Even sophisticated PT/SC is not able to be superior over combined SC and conventional therapy. This is statistically proven, for example, in advanced metastatic colorectal tumours [47].

As an actual example of the need for complexity-oriented approaches in both CT and PT, one is directed to e.g. the presently extended discussions about the "miraculous" effect of medical cannabis [48], treating the symptoms, relieving the pain, decreasing nausea and vomiting, and so increasing the QoL. Currently there is no scientific evidence for these results, but in any case it is unlikely that one single herb could solve the complex problem of PT/SC.

Cancer presents a massive challenge for patients, their families, and their social environment. The medical challenge for professionals is complex, and they have to consider the involvement of SC/PT actions too. A natural consequence of such consideration is to apply it much earlier than the conventional palliative phase. Many aspects of PT are also applicable in conjunction with other treatments from the discovery of the malignant transition [30]. It could be given equal priority alongside diagnosis and treatment [49].

While traditional PT starts when symptom management massively demands it, in the new paradigm early palliative treatment (ePT) starts at diagnosis, in the very early stages [50], and increases its dominance with the expansion of the disease [33]. The integration of ePT into therapy has three levels: linkage, coordination, and full integration [51]. Presently ePT integrated into oncology is in its infancy, while a few clinical trials reveal that ePT may have beneficial effects on QoL [52]. The integration of ePT into the treatment of cancer patients is recommended [53] [54] [55], but presently it is limited mostly to inpatient ser- vices [54] [56] [57]. Due to the complexity of cancerous diseases and the growing number of high-line treatment applications, ePT is having a gradually stronger effect on treatment protocols [58]. Due to this trend, general SC is receiving a growing emphasis and is making the complete process integrative, taking care of patients in its complex unity. At this point supportive and palliative care are united, the ePT component being adequate within the SC, unifying the care domains in physical, psychological, social, spiritual, cultural, end-of-life, and ethical aspects [59]. This integrated treatment approach, one which includes the oncotherapy being integrated with the SC and ePT, is the complex treatment approach (CTA). Cancer causes a complex local and systemic change which needs a complex answer to reestablish the healthy homeostatic control.

Meta-analysis shows that ePT improves the QoL significantly compared to standard cancer-care alone, and no extra adverse effects appeared [52]. ePT de- livered in parallel alongside the conventional standard treatments increases the survival time [60], which together with better QoL is a great support for patients and their families [61]. The American Society of Clinical Oncology (ASCO) gives special attention to ePT too [62], and has expressed the opinion that the optimal care needs to include palliation [63]. There are further efforts requesting the integration of oncology and PT [64]. It is shown that ePT could even start at home. The meta-analysis of palliative homcare shows the benefits, but general attention and the partnership of family and medical professionals have to be improved for its success [29]. The standardizing of PT and the improvement of its quality are general wishes for the new concept of oncology care [65], including for the psychosocial aspects of this activity [66]. More attention to PT practice in rural areas is necessary [67], and in poor countries as well, fitting the actions to the actual availability.

Clinical decision-making requires prognosis estimates, which must include the PT too [68]. Some models for clinical prognosis including PT have been developed, such as the Palliative Prognostic Score [69], the Palliative Prognostic Index [70], and the Glasgow Prognostic score [71].

The harm is relative: "no action" is harmless compared to intervention, but its consequence could be harmful, leaving a disease uncontrolled. The "action" of treatment, however, could cause harm, but compared to the benefit this harm could be evaluated as low. Tumor-oriented "action" in oncology could cause pa- tient-oriented harm, measurable by the quality of life or by acute discomforts, pain, etc., and the clinical evaluation hinges on the harm/benefit (H/B) ratio. The complete process could have a good H/B on average, but with fluctuations the risk of causing a high H/B value could be unacceptable, and thus the "action" not be approved. The decisional fact from a medical point of view is the direction of the changes caused by "action", that is, the results: at the end of the day the patient has to have stable homeostatic control, as near to the usual healthy state as possible. The Hippocratic phrase "nil nocere" ("do no harm") also has to be understood only within this tendency towards dynamism, otherwise the meaning would be "do nothing". The goal of the "action" always has to be pa- tient-oriented as a tendency, or else it is a medical irresponsibility. This evaluation has become central to SC/PT "actions", which have to be integrative parts of the complete therapy. Logically, when this integration of therapies is involved, the ePT concept opens the opportunity to fulfil the need for a complexity of treatment that may lower H/B values. The first line oncotherapies (like surgery and chemo- and radio-therapy) could fail without ePT. The treatment of pain syndrome by ePT is standard of course, but other factors of this complex approach are frequently absent. Indeed, presently most CTA interventions are missing in first line treatments, which can drastically decrease QoL, and this contradicts the patient-oriented dynamical expectations for H/B too.

As well as the use of ePT in seeking to implement the CTA process, the direct optimization of H/B requires natural additions to the active medical intervention. It is general nourishment that insures the basis of the complex treatment approach's potential.

2.2. The Challenge of Nutrition

Life is not in a state of static equilibrium, it is permanently undergoing dynamical changes, an everlasting transformation of energy intake maintaining the equilibrium. We have to quote Albert Einstein who formulated it very simply: "Life is like riding a bicycle: to keep your balance, you must keep moving" [72]. The energy intake comes from the environment and is focused on nourishment. As another Nobelist (another Albert), Szentgyorgyi, formulated the situation: with life-energy it is unimportant that the monkey goes through the jungle; the important thing is that the jungle goes through the monkey, in the form of nutrition, water, and oxygen [73]. The jungle becomes a part of the monkey and in this manner all the living objects there are interconnected; we cannot discuss the energy-cycle of a species without considering the energy-cycle of the other lives in its environment. To maintain all the energy cycling functions of a healthy organism, well optimized, enzyme catalysed biochemical reaction cycles are a must. Nutritionally available micro- and trace elements (Se, B, Ni) or mesoelements (Zn, Cu, Mg) are important cofactors in the catalytic centres of these proteins. In this regard, inconclusive evidence points to the beneficial effect of Zn and Se supplementation in treatment settings for some cancers, especially for an increased quality of life [74] [75].

The culinary and medicinal use of spices and herbs has long been a part of human culture. Presently one major focus regarding diets is weight-loss, variants of which entail extreme selections of foods (like the Atkin's diet, for example). The direction of diets can be in another direction too, to keep the healthy state permanent (like the ketogenic diet), and a third direction is that of special diets to prevent and/or cure various diseases. Comparison of the various diets shows well that the extrema are not helpful in any situation [76], emphasizing the popular knowledge that "the difference between medicament and poison is only the dose". The uncontrolled take of pSC drugs causes adverse effects at incorrect dosing. For example, the extra high dose of fat-soluble vitamins (like Vit. D and E) could cause severe adverse effects, or the high dose of ion-support could produce severe alkaline-acid imbalance.

Due to the complexity of the reactions in living objects we expect well defined negative feedback mechanisms with promoter and suppressor components balancing to a dynamical equilibrium. Over- or under-dosing hurts this balance, favouring one or other of the regulatory sides, destroying the equilibrium and so acting against the homeostatic control. However, it is not only the dosing that causes dietary challenges, but also the complex variety of the nutrients needed [77], healthy homeostasis requiring a diverse nourishment containing all the supporting components in the necessary amounts for the complex processes of living.

The compounds in plants have boosted research interest towards the protection and maintenance of human health and the treatment of some previously untreatable diseases [78]. Phytochemicals in plant materials have attracted interest among scientists, producers, and consumers and have given rise to a new scientific approach, phytochemical research, and on this basis a new industry has arisen. A discipline of phytomedicine has appeared, emphasizing the therapeutic value of herbal medicine [79].

The development of the nutraceuticals field drives phytomedicine's emergence, with even the reactivation of ancient culinary cultures [80]. It makes use of the traditional values of the omnivorous feeding of hunter-gatherer humans along with modern pharma-productions and with public reference to healthy nutraceuticals too. The research in this field stimulates the industry and is also actively incorporated into human healthcare and the pursuit by individuals of healthy lifestyles. A harmony is sought as historic medical experience (famously represented by the Far-Eastern herbal culture) and up-to-date medicine are amalgamated, in the realization that not only the target (i.e., the human homeostasis [81]) but also natural medicines and the products derived from them are complex; phyto-products cannot be regarded as simple, single chemical compounds.

Traditional medicine in the Far-East, including China, India, Korea, and Ja- pan, is traditionally popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. The natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active substances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their simple standardized production is impossible. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phytochemical products, but also in human individuals too, who

show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. From the metabolic point of view the herb-derived products can be categorized into defined groups: carotenoids, alkaloids, poly- phenols, organo-sulphur, and nitrogen compounds [83].

An increasing body of scientific literature suggests that dietary components may exert cancer preventive effects [84]. Tea, soy, cruciferous vegetables, and other foods have been investigated for their cancer preventive potential. Diets rich in polyphenols could help as prophylactics [85] [86]. However, the over- dosed consumption of polyphenols could induce possible harm too [87]. The potential harm of some polyphenols leads to international regulations recommending safe levels for polyphenol consumption [88], but the appropriate dosing limit is debated [89].

Prevention-related nutritionally available mediator and hormone-like molecules such as the long-chain omega-3 polyunsaturated fatty acids (O-3s), such as EPA Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) must be accounted for. Humans need O-3s for optimal functioning at every stage of life [90], as well as their anticancer effects are also being investigated [91] [92]. Another formerly neglected, but recently rediscovered hormone-like substance, Vitamin D3 also belongs to supportive nutritional mediators of the immune system. In a recent meta-analysis of 52 trials with more than 75,000 cases, Vita- min D3 supplementation reduced the risk of cancer death by 16% [93] [94] Hypovitaminosis D is associated with a worse prognosis in breast [95] [96] [97], lung [98], colon and thyroid cancer [93] [94]. There is a significant linear dose relationship between the active metabolite 25OH-D-vitamin levels in blood and overall survival in breast cancer patients. Like all other actions, balance is needed for the maintenance of homeostatic equilibrium [99] [100].
The human body lives in symbioses with a large number of bacteria. The number of these single-cell organisms is greater than the overall number of the cells in tissues of the human organism [101]. A major part of these are gut-bacteria (microbiome) which make a contribution to healthy balance as well as to diseases and immune-disorders [102] too. Intestinal homeostasis is an integrative part of the whole body's well-being [103]. Many nutrients are "pre-digested" before their further digestion for human use, as well as the symbiosis making a contribution to general metabolic processes too [104]. There is an emerging re- search interest in the interaction of polyphenols with microbiota [85], but the present knowledge is insufficient to decide upon the optimal polyphenol intake for maximal health benefit [103]. Despite the field demanding intensive research in recent years, the prospects are great, and the modulation of the microbiota by polyphenols is one greatly focused upon [105].

Other important factors in phytomedicine are the soy phytoestrogen isoflavones Genistein and Daidzein, expected to be potent anticancer ingredients of the daily diet of eastern countries [106]. Traditional Chinese medicine favours the medical plant Astragalus too, due to its antiviral [107], anti-inflammatory [108], and antioxidant [109] properties. These properties, with an immuno-stimulative effect, make it useful for anticancer application too [110].

The traditional medicine of the Far-East, including China, India, Korea, and Japan, is historically popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. From the metabolic point of view, herbally derived products can be categorized into defined groups: the carotenoids, alkaloids, polyphenols, and organo-sulphur and nitrogen compounds [83]. As previously stated, the natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active sub- stances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their standardized production is far from simple. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phyto- chemical products, but also in human individuals, who show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. Despite the underlying mechanisms of the effects of gut microbiota on personal homeostasis in humans being largely unknown, some hints on the regulation of metabolism have recently been published [111].

One important step ahead to accept the achievements of the traditional Chinese medicine (TCM) was the awarding of the Nobel Prize to three co-recipients in 2015 for the medicament named Artemisinin (isolated from the plant Artemisia annua, sweet wormwood) which treats malaria [112]. The history of this discovery shows well the general challenge of the complexity of phytochemical products: the basic discovery was made by the Chinese scientist Tu Youyou, using an herb from the vast range in TCM. It was helpful for malaria, but it was quickly recognized that the malaria parasites soon develop resistance to it, so the WHO terminated its certificate [113], asking producers to halt sales. Subsequent research later developed a Nobel-winning

combination therapy, based on Artemisinin. Presently the therapy is a world-wide routine treatment for malaria. Some other herbs originated from the TCM and their Japanese versions (Kam- po) are widely used in active cancer therapy [114]. The most accepted member of these is the active ingredient group of Shikonin. Shikonin suppresses the oncogenic pyruvate kinase-M2 (PKM2) [115], reducing the cell proliferation in this aggressive disease, and induces cell death by inhibition of glycolysis [116]. The blocking of ATP supply for PKM2 by Sikonin allows the cytotoxic Ca2+ overload and promotes apoptotic cell death, proven by treating the ductal pancreatic adenocarcinoma [117], and could induce mitochondria mediated apoptosis even in cisplatin refractory ovarian cancer [118].

Polyphenols are involved in a large category of antioxidants. The polyphenol-rich foods, principally fruits and vegetables, are beneficial to healthy life. Most vegetables are rich in flavonoids, which are a branch of polyphenolic compounds and make up a significant part of the human diet, having an- ti-inflammatory activity together with related polyphenolic compounds [119]. Many flavonoids (anthocyanins, flavanols, flavanones, flavones, isoflavones, catechins) could suppress the effect of free radicals and arrest the proliferation activity in tumours [120].

Clinical evidence has been collected on the beneficial effects of polyphenols in colon, prostate, epithelial, endometrial, and breast cancer [121] [122]. The early research on polyphenols focused on their antioxidant activity. We will shortly review ramifications of the antioxidant effects of polyphenols here.

The effect of the application in SC of various antioxidants in combination with chemotherapy has been reviewed in a comprehensive analysis [123] showing that antioxidants reduced the side effects and so that these remedies have an exceptional ability to reduce the chemotherapeutic induced toxicity, and to in- crease the QoL and survival time of patients.

Polyphenols can induce mitochondrial adaptation to actual ROS attack [124]. The high antioxidant capacity of vitamins and polyphenols has no overall benefit regarding mortality rate. However, the benefit of these antioxidants in sustaining health is not questioned. The apparent contradiction could be resolved by the assumption that polyphenols are mitochondrial adaptogens, defending the mitochondria from oxidative stress; however it is not a simple reduction of this kind attack, but complexly regulates the mitochondrial biogenesis [124]. Due to the well-known fact that mitochondrial dysfunction has a pivotal role in many diseases, such as neurodegenerative or cardiovascular diseases, and actually having functions in ageing, repairing mitochondrial functioning or at least im- proving its normal activity could have substantial health benefits.

Certain differences in the metabolic processes of malignant and healthy cells have been observed [125] and it is one of the hallmarks of cancer development; in a malignancy a primitive, simple, but fast acting, “old fashioned” metabolism is promoted that produces ATP by a fermentative process instead of by mitochondrial Krebs-cycle, so in this context the most important aspect in the origin of malignancy is a metabolic (mitochondrial) dysfunction [126]. The revolutionary discovery was honoured by a Nobel Prize for Otto Warburg. His idea has been revised [127] [128], and it is enjoying a renaissance nowadays [129], the Warburg effect returning “in a New Theory of Cancer” [130], and new hypo- theses being born on this basis [131] [132]. A malignancy is usually hypoxic be- cause of the intensive fermentative metabolism. This hypoxic environment is a possible selective factor for medical targeting [133].

The response of mitochondria to hypoxic stress is a changing of their sub-cellular localization. The hypoxia ignites mitochondrial fragmentation, forming perinuclear clustering [134] [135] around the nuclei [136]. The hypoxia-induced nuclear relocation of mitochondria is associated with increased nuclear ROS, which can suppress the electron flux and so further increase mitochondrial ROS production [137], and it may allow the ROS signal to directly affect the nucleus. Furthermore, the “wasted” energy of the low efficacy anaerobic ATP production heats the lesion. The increased local temperature helps diffusion processes, as well as inducing higher blood flow and supporting the permeability of the vessel walls. The diffusion coefficient depends linearly on the temperature [138], so the diffusion of intra- and extracellular electrolytes is likely to be higher than in healthy counterparts. The development of ROS has again a complex balance, showing that the way bactericide antibiotics act is possibly connected to ROS [139]. The regular use of antibiotics could be a risk-factor for cancer [140], and in general has a risk of shortening survival [141]. The main disadvantage of antibiotics is that they do not differentiate between pathogenic and beneficial (gut) bacteria [142]. The homeostatic balance of gut microbiota is essential for anti-tumour responses, and could directly impact tumour outcomes [142]. Again, a complex balance has to be considered; pathogens can cause cancer, but the gut microbiota could impact the immune-system and so the cancer’s progression [143].

Another large and extensively studied category of phytomedicine is that of the mushrooms used for culinary and medical purposes. It has been used in the treatment of infections for centuries, and is very popular in Far Eastern medicine. In recent decades medical mushrooms have been a part of the regular treatment of cancer in China and Japan [144]. Presently medical mushrooms are in use in more than 100 medical applications [145]. Two of the crucial ingredients of these are Polysaccharide Krestin (PSK) and polysaccharo-peptide (PSP), also used recently in Western medicine too [144]. PSP is a protein-bound polysaccharide extracted from the edible mushroom Coriolus versicolor [146]. Hundreds of studies have been conducted on the immuno-stimulating and anti-tumour effects of mushroom polysaccharides [138].

The active ingredient of the mushroom Grifola frondosa (Maitake) is a protein-bound polysaccharide, a bioactive extract (proteoglucan) [147]. The purified soluble b-glucan has immunomodulatory and anticancer activity [148] [149] and could inhibit metastases [150]. It stimulates immune activity in experimental models [151]. It has synergetic effects with vitamins, especially when it is intravenously applied [152], as well as increasing bone marrow colony formation, reducing the toxicity of doxorubicin [153].

The mushroom Lentinula edodes (Shiitake) improves gut-immunity and well reduces inflammatory symptoms [154]. A clinically approved intravenous pharmaceutical for third stage gastric cancer with the active ingredient branching polysaccharide, beta-1,3-1,6-D-glucan. Lentinan has been on the Japanese market between 1984 and 2004, manufactured by Ajinomoto and then Taiho Pharmaceuticals. It was successfully applied for inoperable gastric cancer treatment in combination with some chemotherapies [155], but later was withdrawn due to skin-related side effects. L. edodes also showed antiviral activity [156] and immune support [157], as well as improvement of quality of life being observed when it was applied complementarily to other cancer immunotherapies [158].

The mushroom Ganoderma lucidum (Reishi) helps prolong cancer survival [159] in adjunct to conventional treatment to potentiate conventional therapies, enhancing tumour response and stimulating host immunity. Reishi shows immunomodulation in cancer [160] and enhances the response of the tumour [159]. However, its toxicity is also measured on leukocytes [161], as well as hepatotoxicity also being detected [162] [163]. There are some other commonly consumed medical mushrooms, such as Agaricus bisporus (button mushroom) [164] [165], Agaricus blazei (almond mushroom) [166], and Pleurotus ostreatus (oyster mushroom) [167], which are nowadays studied intensively [168] [169].

Various forms of mistletoe extract (Helixor®, Iscador®, LektinolTM, Cefalek- tin®, Eurixor®, etc.) are extensively applied in various cancer treatments [170] [171]. Its immune-stimulating effect probably plays a pivotal role in its anti- cancer applications [172], which is probably combined with a tumour-inhibitive action as well [173]. Again complex in its action, balancing the dose for proper homeostasis is of great importance in mistletoe administration too: it could be found to be anti- or pro-proliferative, depending on the dose [174].

A relatively cheap and effective drug of natural origin is the Metformin, which is a long time accepted first line standard clinical drug to treat type 2 diabetes. It was developed from a natural product, Galega officinalis as the natural source of galegine, used for natural medicine [175]. Metformin is a guanidine analog, product in the synthesis of N,N-dimethylguanidine [176]. It was recently observed that application of Metformin in cancer treatment lowers the incidence of tumor development and the risk of mortality [177]. Studies proved the direct antitumor effect of Metformin, by inducing apoptosis and suppressing the malignant. It was tried for various cancers like breast [178], lung [179] and leukemia [180]. Metformin limits the mitochondrial respiration [181] and it works like the energetic stress on the cell.

The largest and most popular, broadly applied pSC group of remedies are the antioxidants. Antioxidants in their simple chemical meaning are reducing agents, taking up electrons in their reactions. Blocking oxidation is a negative when we consider that this is the fuel of energy in life, ATP being produced by oxidative phosphorylation in mitochondria in most eukaryotes. This energy-production is highly efficient, but can produce a natural by-product, the reactive oxidation species (ROS), which has an important role in homeostasis [182]. The ROS is formed as a by-product of the normal respiration process in mitochondria, as well as being produced by inflammatory processes and the myeloperoxidase action in defence mechanisms. A great many adverse reactions of conventional therapies produce ROS extensively, causing oxidative stress. The ROS, highly reactive compounds definitely being toxic in some cases, can cause significant oxidative damage of cellular structures. Antioxidants could be used as a precious tool in blocking the toxic effects of ROS. The control of ROS could have great potential in complementing chemotherapies to increase their therapeutic efficacy and decrease their toxicity [183], regulating the redox balance between oxidants and antioxidants.

Antioxidants naturally exist as vitamins, minerals, and other compounds (like polyphenols) in foods. Vitamins are natural antioxidants, too, being essential for health. Vitamin therapies are most frequently applied in the antioxidant role in general use for SC/pSC in oncology practice. The vitamins are used in the broad area of diseases in the complete range of medical activities: prevention, curative treatment, palliative application, and rehabilitation too. Most of the vitamins are taken in connection with nutrition and via the microbiome, because they are not produced naturally in the human body [184]. These can be fat soluble (like A, D, E, K vitamins) or water soluble (like ascorbic acid, pantothenic acid, folic acid, niacin, riboflavin, cobalamin, pyridoxine, thiamine, biotin). The early recognition of the importance of vitamins occurred at the beginning of the last century [185] and is currently subject to critical evaluation [186].

The application of antioxidants in cancer prevention and cure is widespread among laypersons, and a significant percentage of cancer patients use antioxidants to prevent malignancy or, very often, apply them during active cancer treatment [187]. Fruits and vegetables are good sources of antioxidants, and it is known that diets high in these sources are healthy in general; antioxidant rich diets are followed for prevention, and presently intensive research is govern- mentally funded [188].

Antioxidant compounds could prevent or delay the oxidation of compounds in life-processes. The discovery of ascorbic acid (vitamin C) was a great step forwards towards understanding the importance of antioxidative action and the redox balance in living systems [189]. Intensive research has identified more vitamins among which are the most known antioxidants among the general population. The proposed mechanisms of vitamins in cancer-prevention and cancer-cure have been discussed and the ratio of the observation and expectations (O/E) of effects of vitamins collected from 102 cancers [190], measuring the plasma-concentration of the A, C, and E vitamins, which have significantly higher observed values than expected in low concentrations of the compounds.

Special attention on the antioxidative effect of vitamin C in cancer treatment has been proposed in a new concept of L. Pauling, a double Nobel Laureate. Pauling proposed using vitamin C to prevent and cure cancer [191]. The proofs of his concept were presented in retrospective clinical trials [192] [193] [194]; however, a placebo-controlled study could not find a similar effect [195] [196], and the method was not approved. Extended and sometimes emotionally heated debates on the antioxidants have appeared in recent research, inducing parallel discussions about general nourishments in which old ideas have been reborn. The application of vitamin C for malignant diseases has recently had a renaissance [197], its effect in cancer therapy being revisited [198]. Phase I clinical trials show its safety and high tolerability [199] [200] [201] and relief from the side-effects of chemotherapy [202]. Clinical trials indicated the efficacy of intra- venous vitamin C (IVC) acting as a potential anticancer therapy and reducing toxic side effects when administered complementarily to chemotherapy [203] [204] [205]. Its dose escalation did not show side effects [206]. Its synergy with chemotherapy improves the QoL [207] [208]. It is also useful for the prevention of malignant diseases [209], as well as suppressing inflammation [210].

Despite the positive results the intensive debate about vitamin C continues [211] [212]. Misconceptions block a clear picture from being formed regarding the situation [213]. These deeply set beliefs have to be understood for progress to be made. All the challenges originate from the clear complexity of the topic. The action of antioxidants has to help in the balancing of the redox status of normal living processes. But inappropriate applications could cause harm, even vitamin C being potentially toxic when applied improperly [214]. It has also been shown, however, that antioxidative supplements confer no prevention of malignancy [215], while other research shows the opposite [216]. Also debate has arisen regarding preventive applications of antioxidants. The role of defensive mechanisms has been discussed in detail [217], a triple step defence activity being com- posed: 1) preventing the formation of new radicals; 2) capturing free radicals to prevent oxidative chain reactions; and 3) repairing the damage caused by the free radicals.

A significant shake-up in the debate around antioxidants was made by another Nobel laureate, J. Watson (the explorer of DNA). Watson published his opinion that antioxidants are harmful, may cause more harm than good, and, contrary to widespread belief, promote cancer [218] [219] [220]. This new turn was an attack not only against the application of vitamin C, but in general against antioxidant treatments in oncology. Extended systemic analyses of the clinical data show increased mortality with treatment using beta carotene, vitamin A, and vitamin E, while vitamin C and selenium had no significant impact on survival [221] [222]. Some evidence has been collected supporting the increased mortality of patients treated with antioxidative therapies [223] [224] [225].

The heated debate was cooled down by opinions that the topic is a double-edged sword [226] [227], and that depending on the cellular concentration and micro-environmental conditions the antioxidant could have both

pro- and anti-cancer potential [228]. Unfortunately, the interaction of antioxidants with anticancer drugs is not understood completely [133], which increases the challenge.

The balance of oxidative stress defines the action of the antioxidants. Many anticancer therapies, including radiotherapy and most chemotherapies, act therapeutically with massive oxidative stress [229]. Supporting the effect of these conventional therapies the naturally present antioxidant defence mechanisms in cancer cells [230] have to be controlled too. This therapeutic approach tries to maximize the oxidative stress in tumour-cells, and the out-balanced redox situation kills them. This approach emphasizes again the extreme complexity (embedded interconnections and self-regulation [231] [232]) of the living sub- stances, where the main goal is the selectivity of cancer cells with oxidative stress, while the heathy cells have to maintain their normal redox balance. The oxidative and antioxidative impacts depend on the concentration of the natural antioxidants, acting like a "double-edges sword" in cancer, in dependence of the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) as one of the transcription factors [109].

The selective factor of electron transfer, a definite clue of oxidative actions [233], could be the hypoxic environment of the cancer-cells [133]. The debate on vitamins in cancer prevention, cure, and palliation is not over yet. Results are promising, but not conclusive [234]. Intensive research and further facts are necessary to harmonize the pro and con opinions. According to our opinion, the doubtfulness is inherent, well showing again the essential complexity of the living structures and their homeostatic balance. As recognized early, the actual homeostasis is personalized [235] and also depends on the mood, and on the actual physiological and psychological condition, as well as on the stresses of the individual [236] [237]. Homeostasis depends on the gut microbiota of the hu- man subject too [238], showing the interdependence of the parts in the symbiosis of human life [239]. To this theoretical consideration, one should add the network-based metagenomic and systems-ecology observations made recently [240]. Clinical analyses show a dependence of cancer [241], especially mucosal cancers [242] [243], on microbiomial composition. These recent reports also clearly support decreasing cancer risks with different preemptive and supportive nutritional manipulations on the microbiome, even in lung cancer [241] [244].

This extreme complexity demands new theoretical consideration, attempting to describe the adaptive dynamics of the phenomenon by cell-population calculations with emphasis on the heterogeneity of cancer cell populations [245]. Systemic-Evolutionary Theory, a new interpretative model of cancer complexity, has evolved [246], as well as the fractal-physiology approach being summarized to explain cancer evolution in connection with metabolism and immunity [247], with the demand of a new paradigm, a new strategy, to win the war against malignant diseases.

Healthy homeostasis struggles to control the malignancy. The first few at- tempts to block the proliferation start intracellularly by controlling the DNA replication. It fails for various reasons, including genetic aberration [248], mitochondrial dysfunction [249], or other intracellular hallmarks of the cancer [250]. An additional challenge is the extracellular factors such as permanent uncontrolled stress (chemical, mechanical, etc.) [251], unhealed wounds [252], inflammation [253], and the extracellular hallmarks of malignancy [254]. The permanent proliferation could be stopped by natural apoptosis, but this mechanism is missing too [255]. Cancerous proliferations and bacteria have a lot in common [256]. The tumour itself has something like an atavism [257], in the sense that the malignant cells act like self-ruled unicellular organisms. The atavism-like process is general, not only with the loss of cellular connections, but al- so with the intracellular genetic structures being altered. The unicellular individualism develops great potential for adaptability to environmental changes, and in fact makes these cells more vigorous than those in the multicellular network. Disorganizing the multicellular structure is the modified genetic activity at the active boundary between unicellular and multicellular areas, promoting primitive transcriptional programs [258]. The malignancy in this general meaning is a distortion of the healthy cellular network, the rules of multicellular organization being broken. The breaking of cellular networks is a general behaviour of all the tumorous cancers independent of their locations in the body (Figure 2). In this sense, the cancer is an organizing (networking) disease, where the cells un- leashed from their networks abandon the living advantages of collectivism, individualism prevailing [259]. The change, however, is not free from new organizing processes, because this unicellular autonomy brings its own requirements regarding environmental conditions for survival [260]; the cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality, strengthening with angiogenesis, injury current, and numerous other supports.

It is interesting to note that the widely applied traditional cancer chemotherapies (anthracyclines) are in fact antibiotics derived from some species of fungi. They are topoisomerase inhibitors and act in the S-phase of the cell-cycle (disturbing the DNA synthesis). Such broadly known and intensively applied antitumour

chemotherapies as Mitomycin-C, Doxorubicin, Epirubicin, Daunorubicin, etc. are all connected to the soil fungi family Streptomyces. In this regard cancer is treated like a bacterial infection, which somehow favours the supporters of atavistic ideas. In fact, a simple atavistic model cannot work in a limited environmental condition; the early unicellular organisms at the beginning of evolution had in fact unlimited nutrients from the environment.

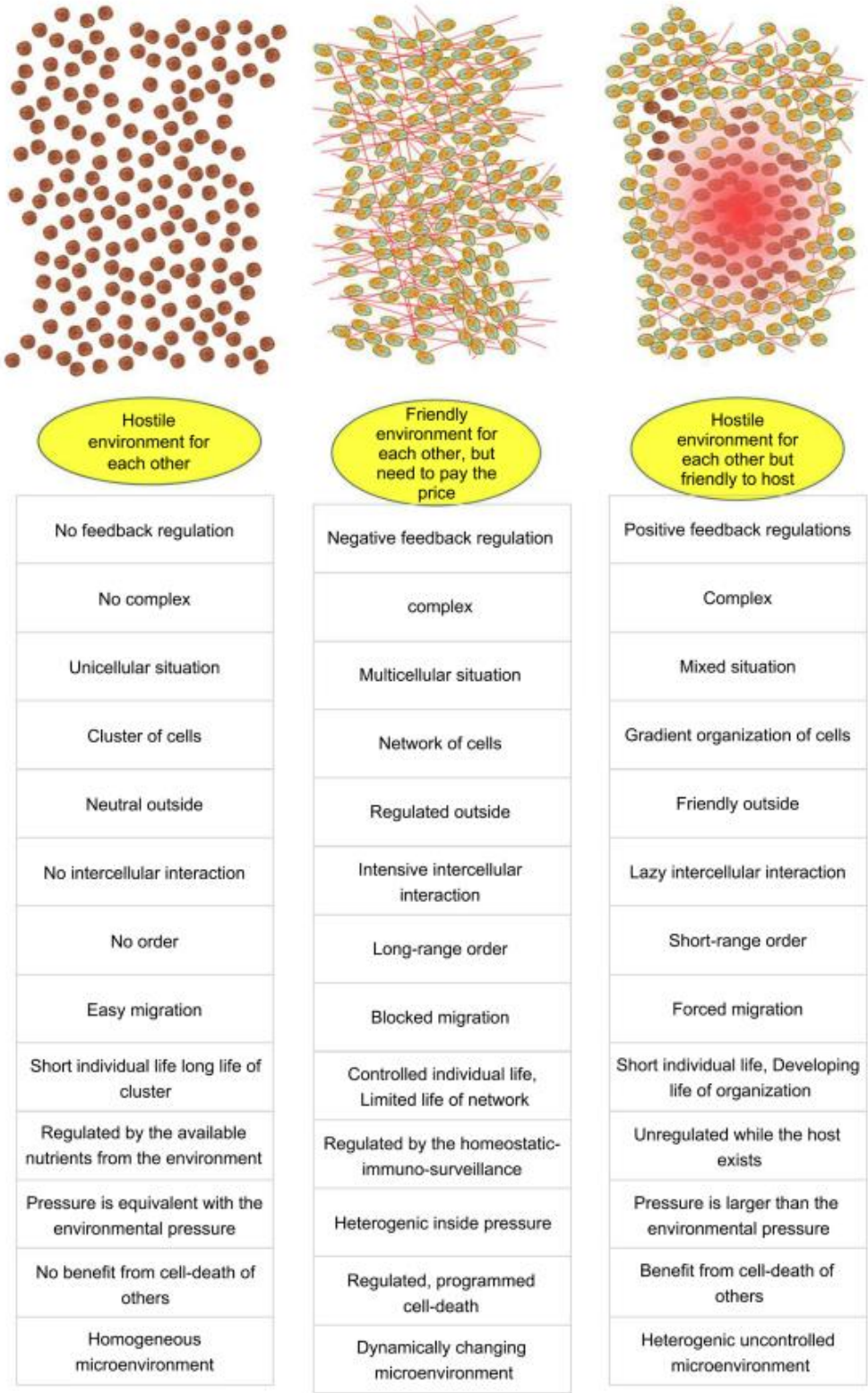


Figure 2. The differences between (a) unicellular living clusters, (b) healthy organized clusters, and (c) malignant clusters of cells. It is clear that the atavistic approach is only formal; the interactions and the organizing of the systems are different.

However, there is knowledge to be gleaned from the atavistic idea: the unicellular organisms were not capable of adapting themselves to broad environmental challenges, their innate adaptive facility was not enough to keep up with environmental developments, and networking started to help their overall survival by work-division, practical networks of cells having a higher survival probability than individuals.
The main development was the adaptive immune system which learned and memorized threats and the protections against them. The atavistic model could be used as a starting point, but this model does not consider all the crucial de- tails (hallmarks) which keep the unicellular units of the cancerous development alive [261]. Both the multicellular networked and the unicellular autonomic states of cells maintain a balance which is probably realized by an electromagnetic route [262]. The FDA-approved TTF also uses this kind of interaction to arrest malignant cell-division [263]. The method of mEHT uses an electrical field to modify the polymerization process [264] with fractal noise modulation for a complex effect. The applied noise is an active harmonizing factor [265], which has an emerging application in physiology [266]. The monitoring of the noise as fluctuations in the complex system could be a factor in its surveillance [267].

The well-structured polymer cytoskeleton is missing in cancer-cells due to their permanent division. The sluggish polymerization of the cytoskeleton [268] [269] promotes huge deformability in cancerous cases [270], cell proliferation being gained with the softer consistency of the cells, which is combined with robustly increased cellular motility [271]. The higher extracellular pressure [272] promotes this higher motility of cancer cells, stimulating the spread of metastases.

The healthy networks are formed mainly by adherent connections in a chain of transmembrane proteins connecting the structure of the cytoskeleton [273] [274]. The protein-chain in the cytoskeleton is a polymerization-like networking [275], where the microfilament structure drastically changes with the electric field [276]. The protein-based networking in the intra and extra cellular milieu is extended with a high-speed network of proton (hydrogen ion) transport. The proton is mostly transported by hydrogen bridges, which allows low energy-dissipation in the transport propagation accompanied by speedy exchange (Grotthuss-mechanism [277]). The proton in this procedure tunnels (jumps) from one water cluster to another through the bridged hydrogen bonds [278]. The lifetime of the H3O+ (hydronium ion) which is involved in this mechanism is rather short (~3 × 10–12 s) so the speed of proton transport is approximately ten times higher than that by diffusion.

To re-establish multicellular networking we have to increase the cooperative driving force, and present a better efficacy of energy-consumption in the net- work than without it. The division of cells themselves does not act against the cooperative networking when it is also regulated by natural controls like apoptosis and differentiation, as in the natural healthy development of organized tis- sues. The structures and the functionality are interconnected [279] and define the dynamisms of the interactions which are always in a critical state [280]. The maintenance of homeostatic equilibrium defines a certain range of parameters of heathy life. The analysing of the huge set of interconnected data has opened a new scientific approach, network medicine, which tries to discover the networking properties of life and of the development of cancer by big-data analysis [281]. The chemical complexity of the human diet is extremely important in regard of living processes with their environmental facilities, and the manner in which life transfers nutrients to its own building-blocks. The huge scale of the chemical diversity of food ingredients and its interactions with the broad spectrum of life remains poorly understood, characterizing a “dark matter of nutrition” [282].

The dynamic interactions in life are complex, but the chemical reactions and the transport of various species as well as the broad spectrum of signal transductions are rather unified in all the living tissues, forming scale-free networks [283]. The living complexity has a self-organized critical state (SOC) limited by the environmental interactions [284]. The dynamical fingerprint of SOC is the well-organized distribution of fluctuations (pink or 1/f noise) [231] [285]. Ap- plied, this fractal noise could be one of the driving forces of reorganization, at least at the interface of the multi and unicellular regions [286] [287]. Usage of this special frequency distribution as a constraint for dynamism could improve success as mEHT does [288]. The electrical current of the modulated radiofrequency delivers the information through charge redistribution [289].

A quotation borrowed by Bjelakovic, Nikolova, et al. [247] from the Chinese military strategist and philosopher Sun Tzu states that “just as flowing water avoids the heights and hastens to the lowlands, so an army avoids strength and strikes weakness”. This philosophical intention, a “target the weakness strategy”, was adopted by Paul Davies and his colleagues [290], showing that one of the weakest sides of cancer’s development is to the immune system. This could be a perfect target instead of the cancer’s main strength, its proliferation. The lack of adaptive immunity to tumours can be revised, and the malignancy is attackable by the host system itself.

The main arrangement of the body remains networked and organized on the homeostatic complexity around the smaller tumours. Multiple robust effects, such as apoptosis and the innate and adaptive immune actions, could be naturally activated to rebuild the overall normal structure. The first step in the regular division of a healthy cell is formally similar to the beginnings of a malignancy: the cell breaks the healthy networking around it and expresses its individual demands for higher energy-intake to perform the delivery of the daughter cells, building up new constituents, creatively doubling the original structure. Its environment during this division is free from the normal networking limitations, and diffusion and osmotic activities are increased, facilitating the necessary transport of nourishments for the development. The electromagnetic properties change in the transition from the networked to the individual state [291]. How- ever, when tumour-cells are clustered, adaptive abilities to the changed conditions are quickly developed. The tumour lesion is associated to an inflammation [292], as was first hypothesized by Virchow in 1863. The inflammatory phenomenon is a critical hallmark of many cancers [253] [293] [294] [295]. The situation is similar to that of a wound which has never healed [252], turning into a chronic injury [296]. After a long period of silence, the inflammatory wound theory is emerging again [297]. The malignant tumour mimics a wound, stimulating the host tissue to support its “healing” [298], avoiding by this “trick” at- tack by the host’s immune surveillance [299]. Contrary to numerous inflammatory immune cells being presented, no immune attack destroys the developing tumour [300]. The malignant cells may hide their individual behaviour from the immune surveillance. The malignant cells develop robust adaptability even to aggressive environmental conditions and also to the attack of natural immune actions. In the case of a developed malignancy even strong natural immune procedures alone are ineffectual. The definite difficulty is that the malignant character of the tumour-cells is hidden and that the immune-cells are not able to recognize these cells as a “disease”; the innate immune-attack and the adaptive immune reaction are absent.

The standard opinion in healthcare at present is that the immune system does not protect against malignant development. However, the absence of any expectation of immune action does not mean that the natural defence mechanisms are beyond consideration. The CTA constitutes a complex treatment, and a variety of antimutagenic factors could be used to prevent the malignant development in its early form or to block the development of new daughter cells in the wide periphery. There are vitamins and micronutrients (often antioxidants), such as vitamins A (in the form of b-carotene), C, D, E, D-glucaric acid, selenium, and uric acid, as well as essential oils [301], that may have roles in cancer prevention, blocking or at least limiting carcinogenesis by interfering with the malignant actions of carcinogens and mutagens as well as of other promoters of cancer development [302]. In this way the inhibitors of malignant initialization and progression become involved in a complex process within the homeostatic dynamism, preventing critical carcinogens in the metabolic processes, detoxifying the tumour-promoting factors, and limiting the possibility of cancer. Or to formulate it in other words, a properly balanced diet could maintain a healthy homeostatic dynamism, avoiding any malignant actions. The effect of course in- volves a complex synergy of diet with lifestyle and environmental conditions, including the avoiding of damaging habits (like smoking, consuming alcohol, etc.) which could negatively interfere with the homeostatic regulation. It has been proven that interferon-gamma with lymphocytes blocks carcinogenesis [303], which in vivo experiment was later evaluated as a “Pillars Article” by Nature [304]. The same group of researchers has published further results on immuno-surveillance and cancer immunoediting [305] [306]. The research, clarifying the role of natural killer-cell (NK-cell) in cancerous processes [307] and the character of regulatory T-cells (Treg) in control of NK-cell activity [308], targets the topic of how the immune-system may prevent the development of malignant processes.

An important topic is the role of gut microbiota in immune reactions, due to a symbiotic complexity of the gut bacteria with the host system in which the transfer of ingredients of nourishment for systemic use is manipulated, which could be used for medical targeting as well [301]. The role of gut microbiota is essential in the actions of the host immune system, working in a complex feed- back frame to ensure the dynamic equilibrium of the homeostasis [309] The biota acts on the initialization of the immune effects, supporting the fight against “intruders” into the system, and has a role in the maturation of the dendritic cells to prepare the defence [310] [311].

There is currently intense research activity focusing on immuno-oncology [312]. This promising research and its medical application has a long history, starting in 1868, observing the protective effects on cancer of intentional inflammation [313], and continuing with various Nobel Prize awarded works in the field of immunology. One of the first theoretical considerations of immune surveillance in oncology was published in 1970 [314]. At this time, check-point inhibitors became the great hope as reagents in cancer therapies [315]. Soon it became obvious again that single-sided action could have serious consequences, causing the opposite effect (hyper-progression) on cancer to that desired [42], connected to immune-related adverse effects [43]. The apparent problem was obvious from the point of view of systemic complexity: a single action may modify

a parameter in the complex balance, but many other conditional parameters have to be considered. The effect could be limited by simple factor too: the majority of the targeted receptors are activated, and the useful effect is saturated [316]. To avoid this problem a low dose check-point blockade has been pro- posed [317].

Due to the frequently mentioned complexity of homeostasis, regular immune surveillance is not the only factor which could act to achieve dynamic equilibrium. When the immune-surveillance does not recognize the malignant tumour, the well induced injury current (see above) may have the possibility to maintain some immune-attacks on the "unhealed wound" by its electromagnetic interactions.

As we have shown above, despite the disability of immune-surveillance to carry out tumour-destructive action in some cases, the general immune status of the patient is important. A well-maintained immune system keeps the general wellbeing of the patient high, could prevent comorbidities, and reduces the side effects of the therapies applied [318], and by these effects the quality of life of the patient is improved. In this sense, general immune support has to be part of the CTA and must be provided as early as the ePT starts.

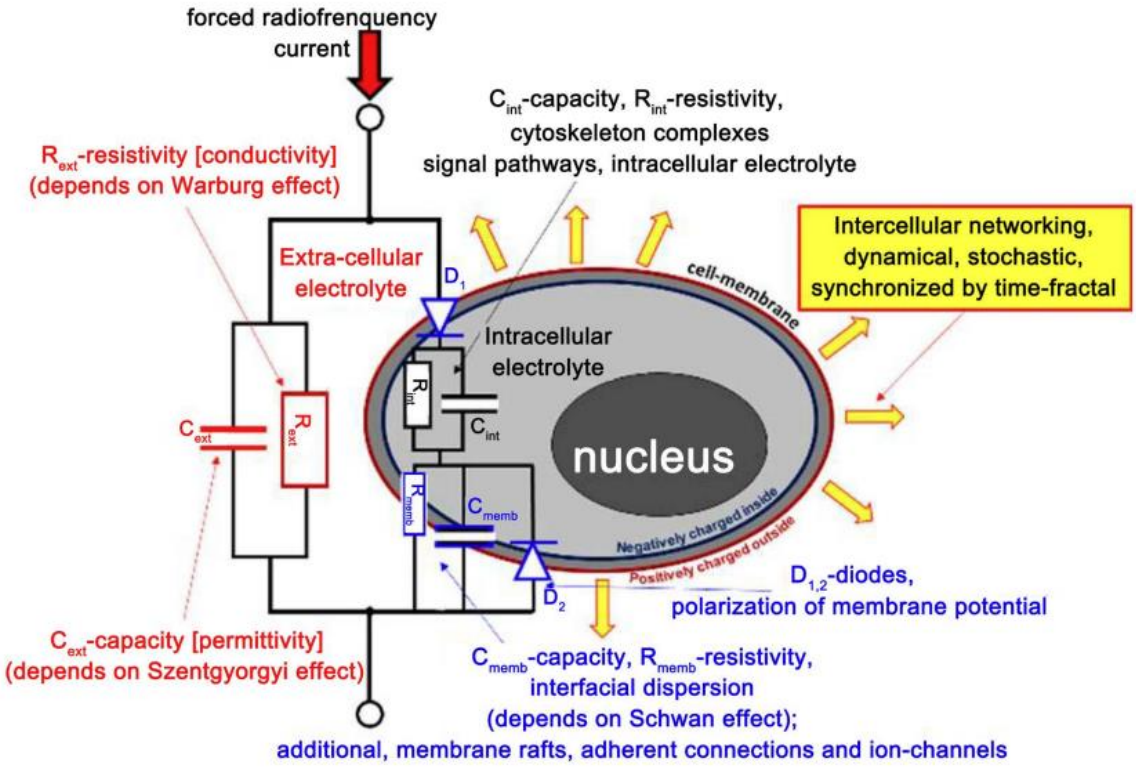
2.3. Electro-Chemical Complexity — A Part of the Supportive and Palliative Care

The largest group of the components of early CTA interventions is comprised of pharma-products [319] [320] [321]. A new kind of treatment is emerging though: the bioelectromagnetic [245] [322]. The properly applied electromagnetic intervention promotes ePT in oncotherapies, as a complementary intervention to conventional therapies in any lines, including in the cases of naïve patients too. The magnetic component of the field established the popularity in these treatments of nano-particle technologies [323], where the energy-absorption can certainly be declared heterogenic [324] in a decisive shift away from the conventional homogeneous heating concept in hyperthermic oncology [325]. The change is not drastic because the traditionally expected temperature homogeneity (isothermal heating) is quasi ensured by the rapid thermal equalization of the target. The selectively targeted nanoparticles heat up their environment, unifying macroscopically the microscopic differences.

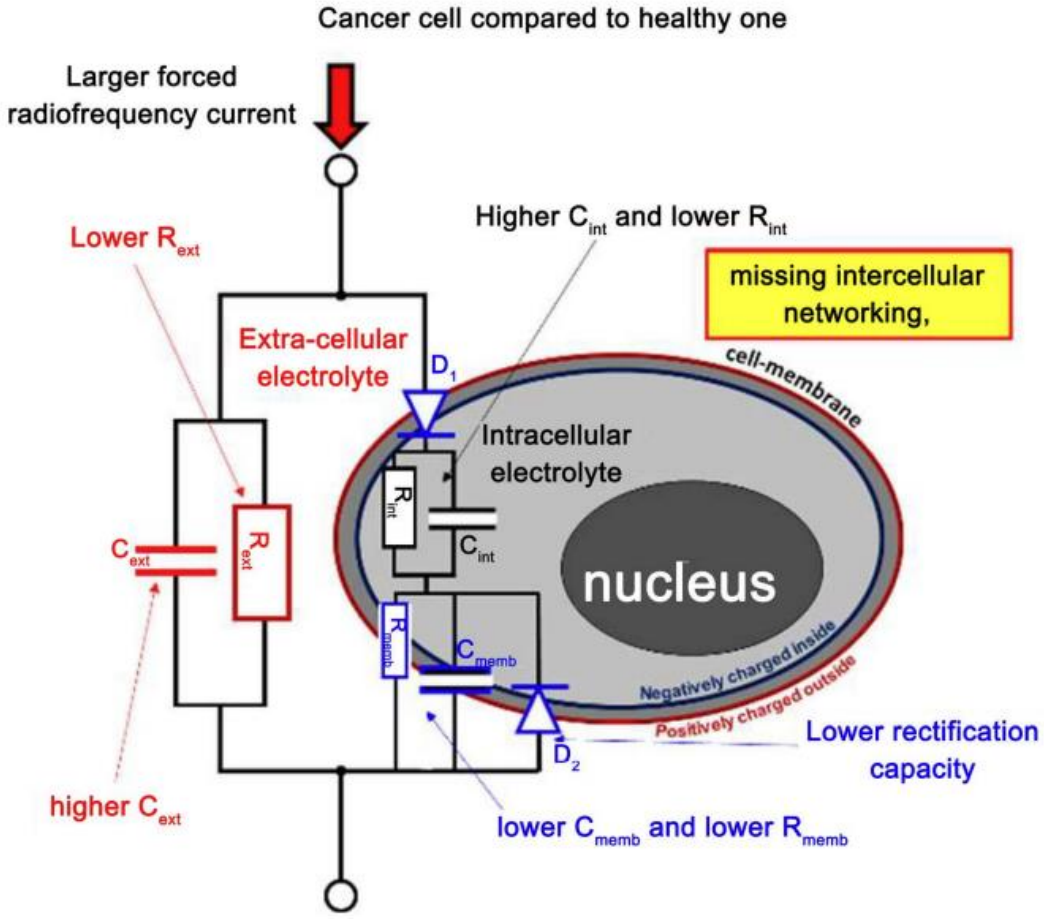
Another nanotechnology method uses the electric field, with [326] or without [327] additional artificial nano-targets, using the absorbed energy of the field. The preclinical results show feasibility in both the artificial [328] and natural [329] nanoparticle targeting methods. The electromagnetic fields effectively arrest the malignant proliferative activities [330] by blocking cellular division [331], developing a complete therapy by an alternating electric tumour-treating field (TTF) [322]. The effect of TTF is clearly shown in clinical practice too [332] [333]. TTF is currently settled as an FDA- and EMA-approved, reimbursed tumor therapeutic intervention. A further advantage of the electric field effect is that it can decrease effusions [334], proven by a clinical trial too [335]. Healthy and malignant cells show a lot of differences from the electromagnetic point of view (Figure 3), giving rise to the possibility of recognizing them by biophysical, bio-electrodynamical methods.

The electromagnetic interactions have the particular advantage of being selective due to the electromagnetic differentiation of the malignant cells from those of their healthy neighbourhood. The more prolific than usual tumour-cells are well distinguishable by their electrolyte structure in the microenvironment of the cells. The malignant proliferation uses a massive amount of nourishments and produces more waste from them too [336]. The ionic concentration increases in the electrolytes where the chemical reactions occur, allowing the recognition of them by their lowered electric resistivity [337]. Furthermore, the characteristically autonomous tumour-cells lose their networking connections, modifying the structure of their microenvironment, and allowing their recognition by this property too [338]. These distinctive characteristics are complexly interconnected [249] and give rise to the special electro-impedance differences between the cells, permitting us to focus the energy on the malignant ones selectively [339]. In this way the absorbed energy shows heterogeneity according to the varied electromagnetic characteristics of the tissues.

There is another advantage of the electric field that could further our attempts to kill the malignant cells selectively [340]. The electrical component of the field is expected to be involved in molecular excitations by the absorption of energy [341] [342]. Using the electric field interactions with the excitable molecules de-fines a principally different nanotechnology, as the nanoparticles are naturally present in the tumour-cells and are used for the desired molecular excitations [343] for the well selected heating of the malignant cells and through these of the complete lesion [344] [345].



(a)



(b)

Figure 3. The electromagnetic difference between (a) healthy and (b) malignant cells is remarkable.

The impedance guided electric field opens a new paradigm of nanotechnologies by the targeting of the excitable molecular branches on the membrane of the selected malignant cells [346]. The selection is supported by the modulation of the radiofrequency carrier [347], a method named modulated electrohyperthermia (mEHT, tradename: oncothermia®) [348]. This method uses the electric field in a precisely selective way [349], there being a strong interconnection of thermal and electrical effects [350]. The transmembrane proteins of cancer cells which assure the interconnections in a healthy network remain un-bonded due to the cellular autonomy in a tumour structure. These proteins form membrane rafts [351], which are highly populated in the membrane of malignant cells [352]. The energy is concentrated on the specific transmembrane proteins clustered in membrane rafts [353], producing the extrinsic excitation of intracellular signals [354].

The excitation of the transmembrane protein compounds helps to ignite variants of apoptotic signal pathways, destroying the tumour by the specific molecular selection of malignancies [355].

The externally oriented energy absorption may choose various pathways:

- caspase independent route through apoptotic inducing factor (AIF) [356];
- extrinsic pathway through caspase-8 (Casp8) and Casp3 [357];
- intrinsic pathway thorough the mitochondria followed by Cas9 and ending on Cas3 [358].

Additionally, the excited Septin4 [359] and Smac/Diabolo [360] proteins neutralize the apoptosis blocker XIAP helping the “avalanche-like” branches of the apoptotic signal to dominate. This complex process reintroduces the sorely missing apoptosis in tumorous development. This apoptotic method has found its way directly from the laboratory to clinical beds [361], being introduced in broad clinical practice [362] [363], and even Phase III trials have been published on electromagnetic methods in oncology [364].

The temperature dependence of the energy-absorption clearly follows the Arrhenius chemical reaction-rate in exponential development by rising temperature [365]. Certain similarities between the temperature dependence and the action of the electric field exist [366], a similar expression of chemical reaction rate being seen in both the solely temperature dependent and the solely field de- pendent cases. The strict similarity of the relationships defines the electromagnetic energy absorption as hyperthermia. The reality of the electromagnetic treatment is that the energy-consumption is expended on a mixture of heating and excitation. Energy analysis of the heating processes shows complexity even in consideration [367] solely from the conventional hyperthermia (heating) point of view. The comparison of conventional and mEHT heating shows well distinguishable differences [368] [369]. The temperature, however, is only a conditional parameter for the phase-transition-like excitation process while the action is physiological [370].
The electromagnetic treatments have further advantages. These are less harmful than the chemo- or radiotherapies and their H/B is lower, so their ap- plication well improves the quality of life of the patients [371] [372], which high- lights again its excellence for the ePT application in CTA therapy. mEHT works complementarily with radio- [373] and chemotherapies [374] [375], increasing its already broad oncological application spectrum. The well applied electro- magnetic therapy solves the long-debated problem of electromagnetic energy-absorption used in oncological hyperthermia [376]. In the conventional mode of electromagnetic energy absorption, the goal is isothermal (homogeneous) heating focused on the tumour as a mass in the body. Unfortunately, this heating affects homeostatic blood-flow, and by this regulation the body tries to re-establish thermal homeostasis by cooling with extra blood from the non-heated part or from the surface of the body. The extra blood-flow, however, could have the risk of supporting the tumour with glucose, this effect thus starting to compete with the anti-tumorous thermal effect. The increased blood-flow around the tumour helps the invasion of malignant cells to the vessels, distant metastases forming by dissemination of the cancer-cells [377], causing controversies in regard of clinical applications in cases where the advantage of thermal cell-killing provided excellent local control but without benefit for overall survival [378] [379]. This contradictory problem has been reported by others too [380] [381] [382]. The results show that it was probably the increased metastases that were causing the contradictions [383]. This contradictory effect of isothermal heating in the traditional hyperthermia protocol is solved by heterogenic heating, attacking the malignant cells by energy, as realized in the mEHT methodology. The selective heating could drastically reduce this risk as the complete mass is not isothermally heated, the energy absorption targeting the malignant cells.

Another electromagnetic effect is the injury current. It is a factor of natural wound healing that is physiological [384]: the injury current, which promotes redifferentiation [385], has a definite role in natural wound healing [291]; consequently, it is used for wound healing [291]. The typical value of the injury cur- rent is approximately 100 μA/cm2 with a voltage drop of approximately 100 mV/cm in an mm extension from the

wound [386]. The weak power of the cur- rent-flow (~0.01 mW/g) does not increase the local temperature [387], but it is measurable during the progression of the wound-healing [388] [389] [390]. This current is physiologically controlled and endures for as long as the wound is healing. The electric field which induces the current determines the orientation [391] and the dynamics of the cell division [392], and it forces cells to migrate [393] to heal the wound [394]. In this way a biological charge transfer promotes the tissue repair [395] [396]. Some invasive [387] [397] and non-invasive [388] [389] [390] experimental results prove the injury current experimentally.

Malignant diseases are systemic. The localization of a tumour is only a visible manifestation but not the complete disease (Figure 4). To achieve a complete cure, the goal has to be increasing survival time, with an acceptable quality of life, of course.

Circulating tumour cells (CTCs) are presented by invasion/intravasation from primary tumours independently of their localization, carrying the risk of metastatic developments. The sentinel lymph-nodes of the tumour are sensitive and vulnerable for the transport of malignant cells from the lesion. CTCs start their dangerous voyage from the very beginning of the malignancy, and the risk of distant extravasation in vital organs grows with time. The goal of conventional local hyperthermia is to eliminate the tumour, seeking the highest goal of complete remission (CR).

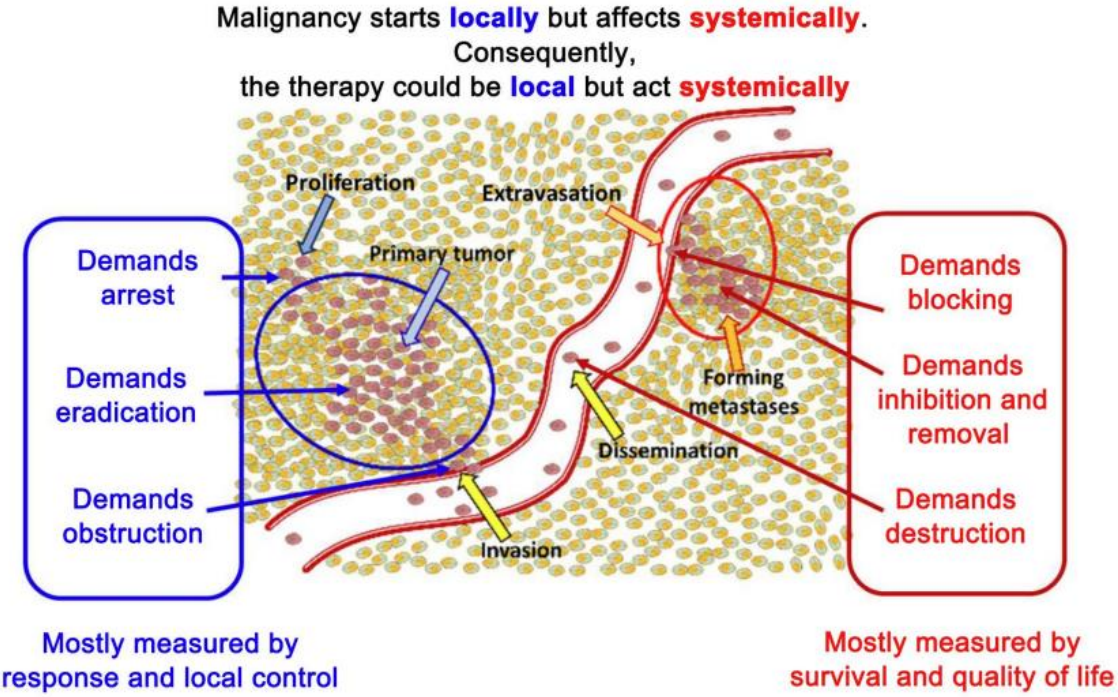


Figure 4. The tumour is a systemic disease; treating only the local tumour does not offer a complete cure, but could achieve a status of "no evidence of disease (NED)", meaning that the diseases is not visible, the malignant lesions remaining but beyond our measuring resolution.

Nevertheless, the disease-free status differs from local measures. The CR alone does not guarantee the clearing of the malignancy from the whole body. This could be the reason that despite improving results with regard to local remission rates, overall survival does not necessarily increase. The development of metastases and/or local relapses considerably limits the patient's overall survival.

The conventional chemotherapies or other systematically administered compounds (check-point inhibitors, enzymes, etc.) target some products and com- pounds of malignant formations, but the process which produces these targets remains intact. Modern cancer-therapy needs a shift of paradigm to focus on the dynamism of the malignancy and to concentrate on the activities which form the malignant phenomena [398]. This new demand again turns our attention to the complexity of the cancer and the living objects which carry it. The previous parts of this article have emphasized the demand for a complex approach regardless of which particularity is being investigated. A review of preclinical and clinical data [399] discovered that several old anticancer chemotherapy drugs, together with radiotherapy, had effects on immune responses. Three categories of immune effects could be identified: 1) direct immune-stimulation of effector cells (like NK and

cytotoxic T-cells), 2) increased immunogenicity to poorly immunogenic malignancies, and 3) blocking the immunosuppressive cells (like Treg). Among others, Gemcitabine was identified as helpful in all categories. Paclitaxel was effective in 1) and 3), and Oxaliplatin was in 2) and 3). Interestingly, even such old drugs as 5-Fluorouracil and Cyclophosphamide were active in categories 2) and 3) respectively, and the antibiotic-related Doxorubicin and Idarubicin were active in category 2). The homeostatic dynamic equilibrium is too complex for outside constraints to be effective in repairing it. Compactly connected feedback mechanisms regulate the system, and the reaction of the homeostatic control will be against any simple restraints. A good example of this is the response to conventional hyperthermia, which aims to kill the tumour by thermal effect. It is a valid aim, but unfortunately homeostatic control mechanisms start correcting this heating by various actions to maintain thermal equilibrium. The most effective reaction is the increased blood-flow and perfusion, pursuing the cooling down of the heated lesion. However, this feedback carries a danger, increasing the delivery of nutrients to the tumour, as well as promoting metastases by cellular invasion to the bloodstream. Consequently, any winning strategy must work together with homeostatic controls, using the natural processes and supporting the immune system in recognizing and destroying the malignant cells throughout the entire body.

Many variants exist that aim to activate personal immune defences against cancer. The key point is the immune recognition of the malignancy. The immune system needs recognizable signs to direct its actions. However, the highly adaptive hiding strategy of the malignant cells protects them from being identified by the immune cells. One effective possibility for the invading of the cancer is the NK cell's innate antitumoural immune action [400] [401]. The NK does not need information by way of MCH-I molecules of the host, and acts in case of a lack of priming too. The cytotoxic activity of NK potentially controls tumour growth [402]. As a component of phytomedicine, Panax ginseng increases NK activity [140]. Complicating the complementing of the available positive effect of NK cells, it might also promote the tumour-progression and angiogenesis [403] inducing a dysfunction by ROS [404].

Also a possibility is to initialize the innate immune action by toll-like receptors (TLR) forcing suitable signal pathways (e.g. through the Tumour-necrosis factor Related Apoptosis Inducing Ligand (TRAIL) and its death receptors (DRs) [405]) to trigger cell death, eliminating the cancer cells [406], as when helping in the fight against infectious diseases [407].

The other possible immune attack could be promoted by adaptive immune reaction. The key is to form antigen presenting cells (APCs) and produce adaptive immune-fighting against the cancer-cells all over the body. The appropriate tumour-specific genetic information has to be obtained from tumours, presenting their malignant behaviour to the immune-surveillance. The process acts through immunogenic cell-death, which is a kind of apoptosis, freeing the genetic information from the tumour. This information may mature the dendritic cells (DCs). The matured DC forms CD4+ and CD8+ (helper and killer) T-cells with appropriate tumour-specific information, preparing them for tumour-specific immune attack. We may realize in this way how to get "back to complexity", as has been recognized as a demand in medicine generally [35].

Complementary mEHT therapy is a perfect tool with which to accomplish the CTA, completing it with appropriate immune support in both the innate and adaptive mechanisms. The heterogenic targeted energy-absorption excites a branch of apoptotic signals, as described above. The main excitation is extrinsic through TLR by TRAIL-R2/DR5, which has the possibility of innate immuno-attack on cancer [408]. The mEHT therapy has an effect on adaptive immune stimulation as well. It produces immunogenic cell death (ICD) with the help of a damage associated molecular pattern (DAMP) [358]. The molecular set of DAMP gives all the necessary tumour-specific information for APC production. The extrinsic signal-excitation triggers the release of calreticulin (CRT, an "eat me signal"), adeno-triphosphate (ATP, a "find me signal"), high-mobility group protein 1 (HMGB1, a "danger signal"), and extracellular heat-shock protein 70 (HSP70, an "info signal"). The APC (mature DC) produces the necessary tumour-specific fighters: the CD4 (helper) and CD8 (killer) T-cells. The maturation of DC cells can be actively supported by the immune-stimulatory effect of b-glucan [409]. It has been shown that the mushroom G. lucidum simultaneously increases the percentages of CD3, CD4, and CD8, with a marginal elevation of NK-cell activity [169]. Assembling and stimulating the immune system against malignancy is a direct way to eliminate the cancer and avoid recurrence and metastases. The activated tumour specific cytotoxic T cells have the ability to recognize and destroy the cancer-cells all over the body. The NK cells, as the front-line defensive fighters, are intensified also by the general enhancing of the immune surveillance. Some cytokines, like IFN-gamma and TNF, could make a decisional addition to the tumour-destructive processes, and in this sense the old kind of anthracyclines [410] and/or electrodynamic therapy like mEHT could boost the immune cells and could create ICD by cytokine response to the treatment. The homeostatic balance is again clear with regard to the DAMP action, which may ignite the tumour-attack but on the other hand may trigger chronic inflammation, promoting tumour-growth [411] [412].

Enhancing the temperature of tumour-cells could increase their sensitivity to immune cell recognition and killing [413]. The naturally developed intracellular heat-shock proteins (HSPs) protect the cancer cells against any attacks, but the expression of them on the outside cellular membrane may activate the NK cells to attack the cell, promoting NK-cell cytotoxicity. When HSP70 is liberated to the extracellular electrolyte, it could tumour-specifically carry genetic information and prepare an orchestrated adaptive immune action against the tumour. In general, an induced immune-effect is observed in mild hyperthermia [414], even in preoperative application too [415]. The cytotoxic activity of NK-cells sharply reduces when the temperature growth is to over 41°C [416] [417], and the general immune activity also drops at over 40°C [418]. Due to the "only local" blocking of immune activity in high-temperature heating, it is neglected in local/regional hyperthermia (LRH) due to an assumption that new immune cells from the non-heated areas will be delivered and substitute for the blocked activity. This effect, however, does not help to form in-situ, real time immune actions. The time delay in presenting active immune-cells in the treated area could be crucial, as genetic information needs to be available promptly for the possibility to mature the dendritic cells to form antigen presentation for a tumour-specific immune effect.

After the precise selection of the clusters, the transmembrane proteins (rafts) on the membranes of the cancer cells absorb the energy [368]. The malignant cells have relatively high raft density compared to their non-malignant neigh- bours [419], helping the selection by this additional factor and the energy-absorption heats the membrane to at least 3°C higher than its surrounding extracellular electrolyte. The full process from the temperature point of view shows the growing temperature to the raft, representing the gradient responsible for mEHT's action [420].

There are a lot of natural compounds, herbal immunostimulants that support the immune system, enhancing its effects [140]. Evidence indicates that several anticancer drugs stimulate the immune system [399]. Antioxidants and phyto- medical compounds, enzymes, etc., are all good candidates for the complex improvement of the immune actions against cancer development. However, again and again we have to emphasize that the homeostatic, healthy complexity needs a balancing equilibrium, that the interconnected feedback mechanisms can be counterproductive, and that a lack of expected benefits or even serious adverse effects can be observed. The complexity could be controlled by dosing (quantity of the taken compounds) and, in the same regard, by their relative applications in dose and time, considering their strong interconnections. One lucky situation is that phytomedical processes (nourishment) involving the taking of herbal and other effectors are usually harmless, because the quantity of the active drugs in the food is generally lower than dangerous levels. High quantity consumption of such nourishments tends to be limited by the stomach's capacity and by healthy lifestyle. However, even natural nourishments are not completely without side effects, especially since interactions between agents can cause side effects, though again, the healthy body will often avoid such problems by quick elimination (usually by the vomiting of drastically interacting contents). The real challenge, which could be dangerous with high dosing of compounds extracted from natural products, is not only quantitative, but deeply qualitative; the homeostatic dynamism is complex in time, and the SOC mechanisms and the fractal interactions redress imbalances in relatively narrow time bands. The observed fractal noise (1/f noise) is the fingerprint of the balance, and its dynamic support could have the same benefit as the variants of herbal or other immunostimulants. This is what is recognized by mEHT, and it applies electromagnetic fluctuations to stimulate the healthy dynamism of the complex interactions. The applied electric field, which transports information to the cellular level, induces chemical changes, but when the energy-absorption is not lethal for the cells by necrosis, it will not cause notable side effects.

The well applied electromagnetic effects are not too strong, causing necrosis by their absorbed energy, and not too weak to cause signal pathway excitations.

Of course, it is frequency dependent, so there is no excitation limit for the zeroth component of fluctuations [421]. The electric field could be associated with in- jury currents, which orients cellular migration and wound healing in general, as was discussed above. In reactions to injury, immune actions have a pivotal role. Injuries produce a higher population of immune cells. Modifying the injury cur- rents could act as a healing factor by physical effects, helping the natural biological processes, which has a probable role in the effect of mEHT too. A continuous injury current, which stimulates cell-proliferation (intending to heal the wound) and promotes the tumour-infiltration of immune-cells, promotes the malignant proliferation [422]. However, the fluctuating current intensity of mEHT and its directional constraint blocks the negative effects of injury cur- rents, blocking the proliferation stimuli.

The primary goal of the local therapies like radiation and local-regional hyperthermia is to eliminate the tumour, measured by the local response of the therapy. Cancer patients with multiple distant metastatic lesions have multiple local therapies as macroscopic tumours are observed. However, most metastases, at least in their early stages, are microscopic, and there is no fine enough resolution of imaging diagnosis to recognize them. A change of paradigm away from these local treatments looks mandatory to solve the consequence of the spreading of malignancy. Intensive research is targeting the challenge to treat distant metastatic lesions even in their microscopic state. The expected appropriate tool to meet these requirements would be a local effect far away from the treatment's actual application location. Radiation generates "danger" signals, transmitting from irradiated to non-irradiated cells, which could lead to off-target effects.

The explanation of radiotherapy by traditional radiobiology has focused on DNA damage to avoid the repair of the targeted tissue. This effect is clearly localized on the irradiated area. The first published observation on a systemic effect of local radiotherapy was made by R. H. Mole, who proposed the term "abscopal effect" in 1953 [423]. The word abscopal is derived from the Latin ab, meaning "positioned away from", and scopos, meaning "a target for shooting at". The abscopal effect is defined as a systemic action of radiation therapy observed in apparently untreated tumour locations distant from the site of irradiation field. These distal effects were neglected for a long time after their first detection; they were "rediscovered" [424] outside the treated field of ionizing radiation [425], but were generally under-recognized in clinical practice [424]. Similar, but certainly much shorter in their effective distance, are bystander effects, which are communicated from an irradiated cell to a non-irradiated bystander cell via cell-to-cell gap junctions [426] or by the secretion or shedding of soluble factors [427] [428]. Important information was provided by case reports showing that despite the radiosensitivity of hypoxic lesion being suppressed, when targeting the hypoxic centre of the tumour the non-targeted bystander area is also affected [429]. The precise nature of factors that mediate the bystander effect is un- known, but reactive oxygen and nitrogen species and various cytokines have been implicated. The short distance bystander information transfer has been ascribed to redox mechanisms, which may produce transmission of ROS, various cytokines, and reactive nitrogen species (RNS), making the off-target response similar to inflammation [430]. The propagation of bystander effects among cancer cells additionally to inflammatory mechanisms involves cellular communication under irradiation with non-uniform dose distribution nearby, and probably immune action in far-away localizations [431].

Radiation-induced long-distance abscopal effects have been extensively documented in several recent reviews [432] [433], which have described both detrimental (e.g., DNA strand cleavage, chromosomal damage, and cytotoxicity [434]) and potentially beneficial abscopal effects. The explanation of abscopal effects has well distinguished it from the bystander effects in the traditional sense [435], having no direct short communication pathway between the treated and untreated cells. Much of the observed physiological abscopal effect has been associated with splenic irradiation [436], but intensive development in using it for solid tumours had been started. In the early period of applications, the ex- planation of the effect related to the immune response mediated by cytokines, but the mechanism remained unclear because this phenomenon was so rare and poorly understood in clinical practice, also giving rise to many controversies [433]; and sometimes being used complementary to other types of local therapies including surgery, hyperthermia, and immunotherapy.

Evidence is piling up that radiotherapy in the appropriate dose stimulates the immune system. In consequence, the abscopal effect has recently been revised, receiving attention as a new therapeutic facility [437]. Intensive application in the clinical setting has been started in a variety of malignancies including lymphoma [438], papillary adenocarcinoma [439], melanoma [440], adenocarcinoma [441] [442], chronic lymphocytic leukaemia [443] [444], lung malignancies [445] [446], and hepatocellular carcinoma [447] [448]. Low-dose radiation de- livers clinical benefits by abscopal effect [449]. The application of emerging immunotherapies by check-point inhibitors combined with radiotherapy has also been tried [450] [451]. This complementary application did not give clear clinical evidence for the benefit of this combination [452] not delivering stable results [453], but the positive promise remains [454]. Despite the incomplete understanding and sometimes controversial results, the present results show clearly the trend of cancer therapy development: cytotoxic drugs used for systemic therapies will be replaced by more complex combined therapies involving the immune-system, providing systemic, abscopal facility [455].

The abscopal effect is probably of the same complex as other living phenomena, tumour-specific mechanisms being seen which are defined by the type of the tumour, and there also being observed general immune responses which could be connected to the distant effects [456]. The role of non-uniform dose could be essential to take account of the mechanism of the distant actions, because it opens a wide spectrum of doses, among which the optimal value need be found from the "offered" quasi-linearly changing dose-spectrum. This is probably the reason why the definitely necrotic ablation technology has observable off-

target effects [457] showing a broad range of electromagnetic interactions, from the necrotic to the weak, negligible effect in the far distance, which may include the necessary optimum for abscopal applications. Probably the same could happen with local high temperature heating too [458]. However, in account of the complexity it is important that the critical homeostatic regulator, the immune system, has a pivotal role in the new paradigm of oncology.

One possible part of the complex approach could be the electrical field, which has no direct macroscopic physiological effects. In in vivo experiments to clarify abscopal effects in rats in combination with radiotherapy, a pulsed electrical field was successfully investigated [459]. These experiments support the idea of trying the mEHT method in the same way, giving reason to expect positive results from the abscopal application of mEHT. The immune-stimulation approach in hyperthermia was well demonstrated earlier [460], and so it is high time to try it with mEHT too. We have to consider also that the old challenge of the homogeneous heating paradigm of conventional hyperthermia, described above, has appeared again using an updated combination of methods: a complex protocol of radiotherapy check-point inhibitors and nanoparticle hyperthermia were applied in a mice model with controversies observed: there was no increase of survival time, and metastatic dissemination to the lung of the model animal was observed [461].

mEHT is immunogenic [462]. Our main idea was based directly on the immune effects of mEHT, which induces ICD by DAMP, as we have shown above. It was however obvious that for a tumour-specific immune action we need APC, which needs a proper immune system, where un-matured DCs are available. An immuno-boosting, as others have used with radiation [463], could be the solution. We report a case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. We learned earlier that a cytokine that activates dendritic cells, the granuloceyte-macrophage colony stimulating factor (GM-CSF) as immune-boost, was earlier used with hyperthermia for inoperable pancreatic tumours with success [460]. The boosting of radiation therapy for abscopal effect used this method too [464] [465] [466]. Following this line, the patient was treated with fractional radiotherapy, modulated electro-hyperthermia (oncothermia), and GM-CSF. The success was significant, and the distant metastases disappeared while the treated primary lung lesion had good shrinking [467].

Our direct goal remained the simple tumour-specific immune attack, as was described above: to develop T-cells to perform action against the malignant cells all over the body, irrespective of their distance from the treated primary lesion [468]. One of the effective methods of inducing abscopal effect starts with ICD [469]. This was clearly demonstrated in murine model in vivo, when the abscopal effect appeared far away from the locally, mEHT treated tumour lesion, all the DAMP molecules of the pattern—CRT, HMGB1, HSP70, and ATP—being measured, and being liberated into the extracellular electrolyte [470]. The model was tried in the situation where the originally available immune system is too weak to produce enough APC. The experiments in vivo showed the excellence of the injection of general un-matured DC-cells to produce clear abscopal effect [471]. Note, the injection of DC cells alone did not show abscopal effect without mEHT application. The immune action works like vaccination, and the re-challenging by the same tumour was ineffective [472]. The vaccination idea was patented [473].

The general abscopal effect by mEHT could be induced not only by DC [471] [472] or GM-CSF immune stimuli [467], as was shown above, but a general treatment complexity including diet and life-style change could work well with mEHT too [474]. Other complex immune-stimuli can be effectively produced by virus application [475] [476], there being excellent case-reports showing the results [477] [478], as well as there being statistically evaluable significance with the serious glioblastoma multiform showing the excellence of the virus-supported mEHT method [479], engineering the bacterial “Trojan horse” [480] to carry out a viral trick. Low-dose check-point inhibition with IL-2 support in combination with mEHT is also successful [481].

A Phase III clinical trial was performed for advanced cervical cancer treated with radio-chemotherapy with and without mEHT [464]. The abscopal effect was also evaluated beside the evaluation of the primary and secondary endpoints [482]; a significant abscopal effect was shown to be induced by mEHT compared to in the control arm. Positron emission tomography-controlled results show clearance of the metastases in the not directly treated pelvic area in more than 25% of the patients, while complete, all disease resolved results were observed in 24% of the cases on the active, mEHT treated arm, compared to just 5.6% in the radio-chemotherapy only control. The result is remarkable, because no extra immune-support was used to obtain these results in such advanced stages.

Elongated survival time, together with the improved quality of life, has been measured with mEHT in many Phase II trials with secondary endpoints of the local response. The joint positive result of the response and survival [362] [479] [483]-[489], even in cases when no conventional complementary treatment was

applicable and mEHT monotherapy was performed [490], indirectly justifies the abscopal effect by the method, which was missing in conventional hyperthermia in many cases.

The best SC and PT depend on many and complex factors. The most important factors to consider:

1) First is the patient's characteristics:
    a) the dosing of the treatment drugs, considering the patient's sensitivity to SC/PT;
    b) general immune status;
    c) kind of disease (morbidity);
    d) stage and severity of disease;
    e) without medical aid, home applied SC/PT.

2) Interactions with conventional, standard treatments:
    a) pharmacological properties of the concomitantly applied standard treatments;
    b) previously applied conventional, standard treatments;
    c) comorbidities, or adverse effects of the applied standard treatments;
    d) biological or physiological reasons for limiting or blocking the standard treatments.

3) Availability of SC/PT in the therapy process:
    a) availability of optimal palliative and supportive drugs;
    b) preparedness and SC/PT knowledge of the medical staff;
    c) sufficient and accepted confidence of the patient in the physician and the therapies prescribed;
    d) availability and intensity of follow-up.

For example, the IV application of high dose vitamin C with mEHT for non-small cell lung cancer was safe [206] had provided significant improvements in a well-selected and controlled cohort of the patients [372]. One of the controlled studies of the best SC for glioblastoma and astrocytoma [486] and pancreas carcinomas [362] shows the necessity of mEHT for significant results [486].

3. Conclusions

The war against cancer [491] is not over yet. There have been many good results and year-by-year new chemotherapies show improvements, but we are far from a final solution. Probably we need a change of paradigm from tumour-oriented therapy strategies to patient-oriented ones and also from product targeted to process targeted treatments, from static distortion to dynamic blockade. The focus of therapy must be reoriented from the products of the tumour (hallmarks, which appear, and are chosen to target) to the process which produces the malignancy [398]. Due to the complexity of the living object the blocking of one product or of a group of them helps only temporarily, because the complex bodily regulation mechanisms soon substitute the absent means for the tumour to develop. We know very well that a single finger as a barrier to overflowing water cannot stop the process itself; we must act at the source of the flow.

We have to stop concentrating on the tumour alone and instead focus on the integrity of the patient. Integrative thinking is necessary with regard to the com- plex structure of life-processes. We believe that, as mathematics has no "alternative mathematics", medicine also has no alternative medicine. When we see the limits of current medical approaches, we have to change the paradigm to meet the challenges. Treatments, and not just medicine, could have alternatives, forcing us in the same direction: towards regarding the patient as a whole, integrative unity.

We propose three goals as a result of this "prospective review":

1) An early palliative therapy should support the conventional therapies, in- creasing their effects together with decreasing their adverse effects. This has to be a part of the CTA, using early palliation and vigilant supportive care. This point must be measured according to the elongation of survival time with im- proved quality of life.

2) Care should be taken to restart and replenish the hampered immune system, which is below its normal capability due to cytostatic effects and disease burden resulting in overloaded immune functions. This refers not only to the possibility of inducing the desired abscopal effect, but to general surveillance too, avoiding comorbidities and new challenges generally in the life-quality of the patient.

3) Complete the revitalization of the immune-system and the whole body in the follow-up period. This goal contains physiological, psychological, and social components too, helping to form a new and convenient lifestyle for the patient.

The key to the new paradigm is the helping of natural complex processes to solve the challenges, and not forcing upon the system something which explodes the homeostatic dynamic balance and which causes the body's regulatory mechanisms to fight against the applied treatment.

There are some desired rules on how to discuss the problems of herb–drug interactions with cancer patients [492]:

- Clarify what type of herbs the patient takes regularly, counting that some herbs are considered as food or spices, and the possible similar ingredients in these that could have a commutative effect;
- The health professional has to have an open mind, not refusing immediately those herbs which have no proven useful effect. Concentrate on the explanation of proven negative effects. Despite few herbs having evidence of useful- ness in treating malignancies, some of them may help relieve symptoms, and many eases the psychological pressure on the patient;
- When the herb has proven disadvantages, explain for the patients why it is so (for example, it reduces the effectivity of the applied therapy or increases the side-effects, or interacts with other useful herbs in a negative way). It is of great help when a similar herb without contraindications can be proposed;
- Educate the patient on the general pros and cons of supplementary drugs;
- Monitor the adverse effects of the herbs which you have agreed to their taking during the therapy and follow-up period;
- When there is no choice of herbal supplements, other therapies like meditation, yoga, or acupuncture could be suggested to improve the quality of life of the patient;
- It would be fine to refer to a specialist who could make a professional balancing of the risks/benefits of the supplemental therapies, and who could offer herbal therapy in the specific circumstances, properly considering the cancer therapy.

All preventive steps have to concentrate on a healthy lifestyle, including a well-balanced diet, care for acid-alkaline balance with intensive liquid consumption, regular daily exercises, and low chronic stress. Nevertheless, the acute daily stresses could be helpful [493] [494]. The hypothalamus-pituitary gland-adrenal-glands (HPA axis) has a complex homeostatic dependence [495]. Its primary function involves the body's reaction to stress involving the sympathetic nervous system and could involve the psychological self-suggestion [496]. The healthy circadian rhythm also affects the HPA axis [497]. Consequently, physiological and psychological health is strongly connected and has an essential role in preventing cancer. No further preventive action is required in the case of a well-working immune system and balanced psychologic status. The homeostatic surveillance actively regulates.

We may follow how the change in paradigms has been mirrored in the adjudgment of oncological hyperthermia:

1) First cames the conclusion regarding unsolved challenges in early applications: "The mistakes made by the hyperthermia community may serve as les- sons, not to be repeated by investigators in other novel fields of cancer treatment" [498].

2) "The biological effects are impressive, but physically the heat delivery is problematic" stated an editorial of the European Journal of Cancer in 2001 [499]. They invoked a shortage of technical knowledge: "The biology is with us, the physics are against us".

3) Later, when no significant development was possible in technical solutions, physiology became the target: "The biology and the physics are with us, but the physiology is against us" [500].

4) In a recent physical analysis of mEHT [347] it was well formulated, as emphasized in two conferences as well, that "physics is our friend, but we have not noticed it" [501] [502].

We have to conclude that the new paradigm is the way back to complexity, using biology, physics, and physiology in their interconnection. Nature takes no consideration that we have divided the phenomena into categories and disciplines, and natural processes involve all aspects, which we are not able to consider in such complexity as is the reality. Cancer as a phenomenon does not distinguish between the human-created disciplines. It is as complex as all the nature around us. We may surmount the gap of the missing complexity by modulated electrohyperthermia (mEHT), answering the question as to "where medicine went wrong" [35]. Thinking on the hyperthermia paradigm has to be complex like the malignancies it aims to treat. The mEHT treatment has shown a wide range of applications from in the laboratory to the clinic [361]. A clinical review was recently published [363] showing excellent results in advanced diseases, mostly in cases where the conventional protocols offer palliation only.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Improving Supportive and Palliative Care for Adults with Cancer—The Manual. National Institute for Clinical Excellence. https://www.nice.org.uk/guidance/csg4

[2] Zafar, S.Y., Currow, D.C., Cherny, N., et al. (2012) Consensus-Based Standards for Best Supportive Care in Clinical Trials in Advanced Cancer. The Lancet Oncology, 13, e77-e82. https://doi.org/10.1016/S1470-2045(11)70215-7

[3] Cancer Supportive Care Drugs Market Size US$ 21.8 Bn by 2026. https://www.globenewswire.com/news-release/2019/07/02/1877384/0/en/Cancer-Su pportive-Care-Drugs-Market-Size-US-21-8-Bn-by-2026.html

[4] Cancer Treatment and Survivorship, Facts and Figures 2019-2021. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistic s/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survi vorship-facts-and-figures-2019-2021.pdf

[5] Rohdenburg (1918) Fluctuations in the Growth Energy of Tumors in Man, with Esspecial Reference to Spontaneous Recession. Journal of Cancer Research, 3, 193-225.

[6] Fauvet, J. (1964) Spontaneous Cancer Cures and Regressions. Revue du Praticien, 14, 2177-2180.

[7] Boyd, W. (1966) The Spontaneous Regression of Cancer. Charles Thomas, Springfield.

[8] O'Regan, B. and Hirschberg, C. (1993) Spontaneous Remission: An Annotated Bibliography. Institute of Noetic Sciences, Sausalito.

[9] Hobohm, U. (2005) Fever Therapy Revisited. British Journal of Cancer, 92, 421-425. https://doi.org/10.1038/sj.bjc.6602386

[10] Cole, W.H. (1976) Spontaneous Regression of Cancer and the Importance of Finding Its Cause. National Cancer Institute Monographs No. 44, 5-9.

[11] Hobohm, U., Grange, J. and Stanford, J. (2008) Pathogen Associated Molecular Pattern in Cancer Immunotherapy. Critical Reviews Immunology, 28, 95-107. https://doi.org/10.1615/CritRevImmunol.v28.i2.10

[12] Zahl, P.H., Mæhlen, J. and Welch, H.G. (2008) The Natural History of Invasive Breast Cancers Detected by Screening Mammography. Archives of Internal Medi- cine, 168, 2311-2316. https://doi.org/10.1001/archinte.168.21.2311

[13] Cole, W.H. and Everson, T.C. (1966) Spontaneous Regression of Cancer. WB Saunders, Philadelphia.

[14] Everson, T. and Cole, W. (1968) Spontaneous Regression of Cancer. JB Saunder & Co., Philadelphia.

[15] Challis, G.B. and Stam, H.J. (1990) The Spontaneous Regression of Cancer. A Re- view of Cases from 1900-1987. Acta Oncologica, 29, 545-550. https://doi.org/10.3109/02841869009090048

[16] Hobohm, U. (2001) Fever and Cancer in Perspective. Cancer Immunology, Immunotherapy, 50, 391-396. https://doi.org/10.1007/s002620100216

[17] Coffey, D.S., Getzenberg, R.H. and DeWeese, T.L. (2006) Hyperthermic Biology and Cancer Therapies: A Hypothesis for the "Lance Armstrong Effect". JAMA, 296, 445-448. https://doi.org/10.1001/jama.296.4.445

[18] Kocasli, S. and Demircan, Z. (2017) Herbal Product Use by the Cancer Patients in Both Pre and Post Surgery Periods and during Chemotherapy. African Journal of Traditional, Complementary, and Alternative Medicines, 14, 325-333. https://doi.org/10.21010/ajtcam.v14i2.34

[19] McCune, J.S., Hatfield, A.J., Blackburn, A.A.R., et al. (2004) Potential of Chemotherapy-Herb Interactions in Adult Cancer Patients. Supportive Care in Cancer, 12, 454-462. https://doi.org/10.1007/s00520-004-0598-1
[20] Weiger, W.A., Smith, M., Boon, H., Richardson, M.A., Kaptchuk, T.J. and Eisen- berg, D.M. (2002) Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer. Annals of Internal Medicine, 137, 889-903. https://doi.org/10.7326/0003-4819-137-11-200212030-00010
[21] Sanson, Fisher, R., Girgis, A., Boyes, A., et al. (2000) The Unmet Supportive Care Needs of Patients with Cancer. Cancer, 88, 226-237. https://doi.org/10.1002/(SICI)1097-0142(20000101)88:1<226::AID-CNCR30>3.0.C O;2-P
[22] O'Connor, M., Drummond, F., et al. (2019) The Unmet Needs of Cancer Survivors in Ireland: A Scoping Review. Irish Cancer Society. https://www.cancer.ie
[23] Boullata, J.I. and Hudson, L.M. (2012) Drug-Nutrient Interactions: A Broad View with Implications for Practice. Journal of the Academy of Nutrition and Dietetics, 112, 506-517. https://doi.org/10.1016/j.jada.2011.09.002
[24] Fradgley, E.A., Bultz, B.D., Kelly, B.J., et al. (2019) Progress toward Integratingdistress as the Sixth Vital Sign: A Global Snapshot of Triumphs and Tribulations in Precision Supportive Care. Journal of Psychosocial Oncology Research and Practice, 1, e2. https://doi.org/10.1097/OR9.0000000000000002
[25] Fielding, R., Lam, W.W., Shun, S.C., Okuyama, T., Lai, Y.H., Wada, M., Akechi, T. and Li, W.W. (2013) For Asia-Pacific Psycho-Oncology Network (APPON) Attributing Variance in Supportive Care Needs during Cancer: Culture-Service, and In- dividual Differences before Clinical Factors. PLOS ONE, 8, e65099. https://doi.org/10.1371/journal.pone.0065099
[26] Need for Supportive Care in Oncology Will Increase during the Next Decade, 13 February 2018. https://www.globaldata.com/need-supportive-care-oncology-will-increase-next-dec ade
[27] Bonevski, B., et al. (2000) Evaluation of an Instrument to Assess the Needs of Patients with Cancer. Supportive Care Review Group. Cancer, 88, 217-225. https://doi.org/10.1002/(SICI)1097-0142(20000101)88:1<217::AID-CNCR29>3.0.C O;2-Y
[28] Chan, A., Lees, J. and Keefe, D. (2014) The Changing Paradigm for Supportive Care in Cancer Patients. Supportive Care in Cancer, 22, 1441-1445. https://doi.org/10.1007/s00520-014-2229-9
[29] Seow, H. and Bainbridge, B. (2017) A Review of the Essential Components of Quality Palliative Care in the Home. Journal of Palliative Medicine, 20, S37-S44. https://doi.org/10.1089/jpm.2017.0392
[30] Johnson, S.B., Butow, P.N., Bell, M.L., et al. (2018) A Randomized Controlled Trial of an Advance Care Planning Intervention for Patients with Incurable Cancer. British Journal of Cancer, 119, 1182-1190. https://doi.org/10.1038/s41416-018-0303-7
[31] Glare, P.A. (2013) Early Implementation of Palliative Care Can Improve Patient Outcomes. Journal of National Comprehensive Cancer Network, 11, S3-S9. https://doi.org/10.6004/jnccn.2013.0212
[32] Thomas, K. (2003) Caring for the Dying at Home. Companions on a Journey. Radcliffe Medical Press, Oxford.
[33] Kaasa, S., Loge, J.H., Aapro, M., et al. (2018) Integration of Oncology and Palliative Care: A Lancet Oncology Commission. The Lancet Oncology, 19, E588-E653. https://doi.org/10.1016/S1470-2045(18)30415-7
[34] Smyth, J.F. (2008) Disclosing Gaps between Supportive and Palliative Care—The Past 20 Years. Supportive Care in Cancer, 16, 109-111. https://doi.org/10.1007/s00520-007-0354-4
[35] West, B.J. (2006) Where Medicine Went Wrong: Rediscovering the Path to Complexity. World Scientific, London. https://doi.org/10.1142/6175
[36] Senn, H.J., Glaus, A. and Schmid, L. (1988) Supportive Care in Cancer Patients. Springer-Verlag, Berlin. https://doi.org/10.1007/978-3-642-82932-1
[37] Palliative Care Definition by WHO. https://www.who.int/cancer/palliative/definition/en
[38] Nwosu, A.C., Sturgeon, B., McGlinchey, T., et al. (2019) Rotobic Technology for Palliative and Supportive Care: Strengths, Weaknesses, Opportunities and Threats. Paliative Medicine, 33, 1106-1113. https://doi.org/10.1177/0269216319857628
[39] Keefe, D., Garni, A., Villalon, A., et al. (2016) Challenges in Supportive Cancer Care: Perspectives from the Asia Pacific and Middle East. Supportive Care in Cancer, 24, 4479-4481. https://doi.org/10.1007/s00520-016-3381-1
[40] Keefe, D.M. and Bateman, E.H. (2012) Tumor Control versus Adverse Events with Targeted Anticancer Therapies. Nature Reviews Clinical Oncology, 9, 98-109. https://doi.org/10.1038/nrclinonc.2011.192
[41] Chan, A., Chiang, Y.Y., Low, X.H., et al. (2013) Affordability of Cancer Treatment for Aging Cancer Patients in Singapore: An Analysis of Health, Lifestyle, and Financial Burden. Supportive Care in Cancer, 21, 3509-3517. https://doi.org/10.1007/s00520-013-1930-4
[42] Brower, V. (2016) Hyperprogressive Disease with Anti-PD-1 and Anti-PD-L1. Clinical Cancer Research, 17, e527. https://doi.org/10.1016/S1470-2045(16)30590-3

[43] Gelao, L., Criscitiello, C., Esposito, A., et al. (2014) Immune Checkpoint Blockade in Cancer Treatment: A Double-Edged Sword Cross-Targeting the Host as an "In- nocent Bystander". Toxins, 6, 914-933. https://doi.org/10.3390/toxins6030914
[44] Sikora, K., Advani, S., Koroltchouk, V., et al. (1999) Essential Drugs for Cancer Therapy: A World Health Organization Consultation. Annals of Oncology, 10, 385-390. https://doi.org/10.1023/A:1008367822016
[45] Markiewski, M.M. and Lambris, J.D. (2009) Is Complement Good or Bad for Cancer Patients? A New Perspective on an Old Dilemma. Trends in Immunology, 30, 286-292. https://doi.org/10.1016/j.it.2009.04.002
[46] MacDonald, N. (2007) Cancer Cachexia and Targeting Chronic Inflammation: A Unified Approach to Cancer Treatment and Palliative/Supportive Care. The Journal of Supportive Oncology, 5, 157-162.
[47] Barni, S., Lissoni, P., Cazzaniga, M., et al. (1995) A Randomized Study of Low-Dose Subcutaneous Interleukin-2 plus Melatonin versus Supportive Care Alone in Metastatic Colorectal Cancer Patients Progressing under 5-Fluorouracil and Folates. Oncology, 52, 243-245. https://doi.org/10.1159/000227465
[48] Kleckner, A.S., Kleckner, I.R., Kamen, C.S., et al. (2019) Opportunities for Cannabis in Supportive Care in Cancer. Therapeutic Advances in Medical Oncology, 11, 1-29. https://doi.org/10.1177/1758835919866362
[49] Welsh Assembly Government (2001) Improving Health in Wales: A Plan for the NHS with Its Partners. Welsh Assembly Government, Cardiff.
[50] Irwin, K.E., Greer, J.A., Khatib, J., et al. (2013) Early Palliative Care and Metastatic Non-Small Cell Lung Cancer: Potential Mechanisms of Prolonged Survival. Chronic Respiratory Disease, 10, 35-47. https://doi.org/10.1177/1479972312471549
[51] Leutz, W.N. (1999) Five Laws for Integrating Medical and Social Services: Lessons from the United States and the United Kingdom. The Milbank Quarterly, 77, 77-110. https://doi.org/10.1111/1468-0009.00125
[52] Haun, M.W., Estel, S., Rücker, G., et al. (2017) Early Palliative Care for Adults with Advanced Cancer. Cochrane Database of Systematic Reviews, 6, CD011129. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011129.pub2/abstract
[53] Hui, D., Elsayem, A., DelaCruz, M., et al. (2010) Availability and Integration of Palliative Care at US Cancer Centers. JAMA, 303, 1054-1061. https://doi.org/10.1001/jama.2010.258
[54] Gelfman, L.P. and Morrison, R.S. (2008) Research Funding for Palliative Medicine. Journal of Palliative Medicine, 11, 36-43. https://doi.org/10.1089/jpm.2006.0231
[55] Abrahm, J.L. (2012) Integrating Palliative Care into Comprehensive Cancer Care. Journal of the National Comprehensive Cancer Network, 10, 1192-1198. https://doi.org/10.6004/jnccn.2012.0126
[56] Goldsmith, B., Dietrich, J., Du, Q., et al. (2008) Variability in Access to Hospital Palliative Care in the United States. Journal of Palliative Medicine, 11, 1094-1102. https://doi.org/10.1089/jpm.2008.0053
[57] Morrison, R.S., Augustin, R., Souvanna, P., et al. (2011) America's Care of Serious Illness: A State-by-State Report Card on Access to Palliative Care in Our Nation's Hospitals. Journal of Palliative Medicine, 14, 1094-1096. https://doi.org/10.1089/jpm.2011.9634
[58] Howie, L. and Peppercorn, J. (2013) Early Palliative Care in Cancer Treatment: Rationale, Evidence and Clinical Implications. Therapeutic Advances in Medical Oncology, 5, 318-323. https://doi.org/10.1177/1758834013500375
[59] Kamal, A.H., Gradison, M., Maguire, J.M., et al. (2014) Quality Measures for Palliative Care in Patients with Cancer: A Systematic Review. Journal of Oncology Practice, 10, 281-287. https://doi.org/10.1200/JOP.2013.001212
[60] Portman, D. and Thirlwell, S. (2015) Perspectives, Progress and Opportunities for Palliative Care in Oncology. Cancer Control, 22, 382-384. https://doi.org/10.1177/107327481502200402
[61] Ramchandran, K., Tribett, E., Dietrich, B., et al. (2015) Integrating Palliative Care into Oncology: A Way Forward. Cancer Control, 22, 386-395. https://doi.org/10.1177/107327481502200404
[62] Smith, T.J., Temin, S., Alesi, E.R., et al. (2012) American Society of Clinical Oncology Provisional Clinical Opinion: The Integration of Palliative Care into Standard Oncology Care. Journal of Clinical Oncology, 30, 880-887. https://doi.org/10.1200/JCO.2011.38.5161
[63] American Society of Clinical Oncology (1998) Cancer Care during the Last Phase of Life. Journal of Clinical Oncology, 16, 1986-1996. https://doi.org/10.1200/JCO.1998.16.5.1986
[64] Cherny, N., Catane, R., Schrijvers, D., et al. (2010) European Society for Medical Oncology (ESMO) Program for the Integration of Oncology and Palliative Care: A 5-Year Review of the Designated Centers' Incentive Program. Annals of Oncology, 21, 362-369. https://doi.org/10.1093/annonc/mdp318

[65] Kamal, A.H., Harrison, K.L., Bakitas, M., et al. (2015) Improving the Quality of Palliative Care through National and Regional Collaboration Efforts. Cancer Control, 22, 396-402. https://doi.org/10.1177/107327481502200405
[66] Jacobsen, P.B. and Lee, M. (2015) Integrating Psychosocial Care into Routine Cancer Care. Cancer Control, 22, 442-449. https://doi.org/10.1177/107327481502200410
[67] Baitas, M.A., Elk, R., Astin, M., et al. (2015) Systematic Review of Palliative Care in the Rural Setting. Cancer Control, 22, 450-464. https://doi.org/10.1177/107327481502200411
[68] Hui, D. (2015) Prognostication of Survival in Patients with Advanced Cancer: Predicting the Unpredictable? Cancer Control, 22, 489-497. https://doi.org/10.1177/107327481502200415
[69] Tassinari, D., Montanari, L., Maltoni, M., et al. (2008) The Palliative Prognostic Score and Survival in Patients with Advanced Solid Tumors Receiving Chemotherapy. Supportive Care in Cancer, 16, 359-370. https://doi.org/10.1007/s00520-007-0302-3
[70] Morita, T., Tsunoda, J., Inoue, S., et al. (1999) The Palliative Prognostic Index: A Scoring System for Survival Prediction of Terminally Ill Cancer Patients. Supportive Care in Cancer, 7, 128-133. https://doi.org/10.1007/s005200050242
[71] Miura, T., Matsumoto, Y., Hama, T., et al. (2015) Glasgow Prognostic Score Predicts Prognosis for Cancer Patients in Palliative Settings: A Subanalysis of the Ja- pan-Prognostic Assessment Tools Validation (J-Proval) Study. Supportive Care in Cancer, 23, 3149-3156. https://doi.org/10.1007/s00520-015-2693-x
[72] Calaprice, A. (2011) The Ultimate Quotable Einstein. Princeton University Press, Princeton.
[73] Szentgyorgyi, A. (1978) The Living State and Cancer. Marcel Dekker Inc., New York.
[74] Yamagata, T., Nakamura, Y., Yamagata, Y., et al. (2003) The Pilot Trial of the Prevention of the Increase in Electrical Taste Thresholds by Zinc Containing Fluid In- fusion during Chemotherapy to Treat Primary Lung Cancer. Journal of Experimental & Clinical Cancer Research, 22, 557-563.
[75] Sieja, K. and Talerczyk, M. (2004) Selenium as an Element in the Treatment of Ovarian Cancer in Women Receiving Chemotherapy. Gynecologic Oncology, 93, 320-327. https://doi.org/10.1016/j.ygyno.2003.12.013
[76] Freedman, M.R., King, J. and Kennedy, E. (2001) Popular Diets: A Scientific Re- view. Obesity Research, 9, 1S-40S. https://doi.org/10.1038/oby.2001.113
[77] Michael, M. (2018) Comparative Studies of Energy Homeostasis in Vertebrates. Frontiers in Endocrinology and Frontiers in Neurosciesnce, 9, Article No. 291. https://doi.org/10.3389/978-2-88945-560-7
[78] Cherif, A.O. (2012) Phytochemicals Components as Bioactive Foods. In: Rasooli, I., Ed., Bioactive Compounds in Phytomedicine, IntechOpen, London, 113-124. https://www.intechopen.com/books/bioactive-compounds-in-phytomedicine/phytochemicals-components-as-bioactive-foods
[79] Sajjad, M., Khan, A., Ahmad, I. and Chattopadhyay, D. (2019) New Look to Phyto- medicine, Advancements in Herbal Products as Novel Drug Leads. Elsevier, Amsterdam.
[80] Pandey, M., Debnath, M., Gupta, S., et al. (2011) Phytomedicine: An Ancient Approach Turning into Future Potential Source of Therapeutics. Journal of Pharmacognosy and Phytotherapy, 3, 113-117.
[81] Hegyi, G., Vincze, G. and Szasz, A. (2012) On the Dynamic Equilibrium in Homeostasis. Open Journal of Biophysics, 2, 64-71. https://doi.org/10.4236/ojbiphy.2012.23009
[82] Barbosa, W.L.R., Pinto, L., Malheiros, L.C.S., Barros, P.M.S.S., de Freitas, C.B., Silva, J.O.C., Gallori, S. and Vincieri, F.F. (2012) Standardization of Herbal Drugs Derivatives with Special Reference to Brazilian Regulations. In: Rasooli, I., Ed., Bioactive Compounds in Phytomedicine, InTechOpen, London, 69-92. http://www.intechopen.com/books/bioactive-compounds-inphytomedicine/standar dization-of-herbal-drugs-derivatives-with-special-reference-to-brazilian-regulations
[83] Lampe, J.W. and Chang, J.L. (2007) Interindividual Differences in Phytochemical Metabolism and Disposition. Seminars in Cancer Biology, 17, 347-353. https://doi.org/10.1016/j.semcancer.2007.05.003
[84] Boik, J. (2001) Natural Compounds in Cancer Therapy. Quality Books, Inc., Oregon.
[85] Cory, H., Passarelli, S., Szeto, J., et al. (2018) The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. Frontiers in Nutrition, 5, Article No. 87. https://doi.org/10.3389/fnut.2018.00087
[86] Oparam, E.I. and Chohan, M. (2014) Culinary Herbs and Spices: Their Bioactive Properties the Contribution of Polyphenols and the Challenges in Deducing Their True Health Benefits. International Journal of Molecular Sciences, 15, 19183-19202. https://doi.org/10.3390/ijms151019183
[87] Eloe-Fadrosh, E.A. and Rasko, D.A. (2013) The Human Microbiome from Symbiosis to Pathogenesis. Annual Review of Medicine, 64, 145-163. https://doi.org/10.1146/annurev-med-010312-133513
[88] Martin, K.R. and Appelm, C.L. (2010) Polyphenols as Dietary Supplements: A Double-Edged Sword. Nutrition and Dietary Supplements, 2, 1-12. https://doi.org/10.2147/NDS.S6422

[89] Hooper, B. and Frazier, R. (2012) Polyphenols in the Diet: Friend or Foe? Nutrition Bulletin, 37, 297-308. https://doi.org/10.1111/j.1467-3010.2012.02001.x
[90] Afonso, C., Bernardo, I., Bandarra, N.M., Martins, L.L. and Cardoso, C. (2019) The Implications of Following Dietary Advice Regarding Fish Consumption Frequency and Meal Size for the Benefit (EPA+DHA and Se) versus Risk (Mehg) Assessment. International Journal of Food Sciences and Nutrition, 70, 623-637. https://doi.org/10.1080/09637486.2018.1551334
[91] Moloudizargari, M., Mortaz, E., Asghari, M.H., et al. (2018) Effects of the Polyunsaturated Fatty Acids, EPA and DHA, on Hematological Malignancies: A Systemic Review. Oncotarget, 9, 11858-11875. https://doi.org/10.18632/oncotarget.24405
[92] Serini, S., Fasano, E., Piccioni, E., Cittadini, A.R.M. and Calviello, G. (2011) Differential Anti-Cancer Effects of Purified EPA and DHA and Possible Mechanisms Involved. Current Medicinal Chemistry, 18, 4065-4075. https://doi.org/10.2174/092986711796957310
[93] Buttigliero, C., Monagheddu, C., Petroni, P., et al. (2011) Prognostic Role of Vitamin D Status and Efficacy of Vitamin D Supplementation in Cancer Patients: A Systematic Review. Oncologist, 16, 1215-1227. https://doi.org/10.1634/theoncologist.2011-0098
[94] Zhang, Y., Fang, F., Tang, J., et al. (2019) Association between Vitamin D Supplementation and Mortality: Systematic Review and Meta-Analysis. BMJ, 366, l4673. https://doi.org/10.1136/bmj.l4673
[95] Hu, K., Callen, D.F., Li, J. and Zheng, H. (2018) Circulating Vitamin D and Overall Survival in Breast Cancer Patients: A Dose-Response Meta-Analysis of Cohort Studies. Integrative Cancer Therapies, 17, 217-225. https://doi.org/10.1177/1534735417712007
[96] Estébanez, N., Gómez, A.I., Palazuelos, C., et al. (2018) Vitamin D Exposure and Risk of Breast Cancer: A Meta-Analysis. Scientific Reports, 8, Article No. 9039. https://doi.org/10.1038/s41598-018-27297-1
[97] Hossain, S., Beydoun, M.A., Beydoun, H.A., et al. (2019) Vitamin D and Breast Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Clinical Nutrition ESPEN, 30, 170-184. https://doi.org/10.1016/j.clnesp.2018.12.085
[98] Zhang, L., Wang, S., Che, X. and Li, X. (2015) Vitamin D and Lung Cancer Risk: A Comprehensive Review and Meta-Analysis. Cellular Physiology & Biochemistry, 36, 299-305. https://doi.org/10.1159/000374072
[99] Hsueh, T.Y., Baum, J.I. and Huang, Y. (2018) Effect of Eicosapentaenoic Acid and Docosahexaenoic Acid on Myogenesis and Mitochondrial Biosynthesis during Murine Skeletal Muscle Cell Differentiation. Frontiers in Nutrition, 5, Article No. 15. https://doi.org/10.3389/fnut.2018.00015
[100] Ochi, E. and Tsuchiya, Y. (2018) Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in Muscle Damage and Function. Nutrients, 10, Article 552. https://doi.org/10.3390/nu10050552
[101] Chow, J., Lee, S.M., Shen, Y., et al. (2010) Host-Bacterial Symbiosis in Health and Disease. Advances in Immunology, 107, 243-274. https://doi.org/10.1016/B978-0-12-381300-8.00008-3
[102] De la Fuente, M., MacDonald, T.T. and Hermoso, M.A. (2019) Editorial: Intestinal Homeostasis and Disease: A Complex Partnership between Immune Cells, Non-Immune Cells, and the Microbiome. Frontiers in Immunology, 10, Article No. 2775. https://doi.org/10.3389/fimmu.2019.02775
[103] Williamson, G. (2017) The Role of Polyphenols in Modern Nutrition. Nutrition Bulletin, 42, 226-235. https://doi.org/10.1111/nbu.12278
[104] Morowitz, M.J., Carlisle, E. and Alverdy, J.C. (2011) Contributions of Intestinal Bacteria to Nutrition and Metabolism in the Critically Ill. Surgical Clinics of North America, 91, 771-785. https://doi.org/10.1016/j.suc.2011.05.001
[105] Singh, A.K., Cabral, C., Kumar, R., et al. (2019) Beneficial Effects of Dietary Poly- phenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. Nutrients, 11, 2216. https://doi.org/10.3390/nu11092216
[106] Spagnuolo, C., Russo, G.L., Orhan, I.E., et al. (2015) Genistein and Cancer: Current Status, Challenges, and Future Directions. Advances in Nutrition, 6, 408-419. https://doi.org/10.3945/an.114.008052
[107] Wang, S., Li, J., Huang, H., et al. (2009) Anti-Hepatitis B Virus Activities of Astragaloside IV Isolated from Radix Astragali. Biological and Pharmaceutical Bulletin, 32, 132-135. https://doi.org/10.1248/bpb.32.132
[108] Wang, Y., Ren, T., Zheng, L., et al. (2016) Astragalus Saponins Inhibits Lipopolysaccharide-Induced Inflammation in Mouse Macrophages. The American Journal of Chinese Medicine, 44, 579-593. https://doi.org/10.1142/S0192415X16500324
[109] Shahzad, M., Shabbir, A., Wojcikowski, K., et al. (2016) The Antioxidant Effects of Radix Astragali (Astragalus membranaceus and Related Species) in Protecting Tis- sues from Injury and Disease. Current Drug Targets, 17, 1331-1340. https://doi.org/10.2174/1389450116666150907104742
[110] Chu, D.T., Wong, W.L. and Mavligit, G.M. (1988) Immunotherapy with Chinese Medicinal Herbs. II. Reversal of Cyclophosphamide-Induced Immune Suppression by Administration of Fractionated Astragalus membranaceus in Vivo. Journal of Clinical and Laboratory Immunology, 25, 125-129.

[111] Martin, A.M., Yabut, J.M., Choo, J.M., et al. (2019) The Gut Microbiome Regulates Host Glucose Homeostasis via Peripheral Serotonin. PNAS, 116, 19802-19804. https://doi.org/10.1073/pnas.1909311116
[112] Miller, L.H. and Su, X. (2011) Artemisinin: Discovery from the Chinese Herbal Garden. Cell, 146, 855-858. https://doi.org/10.1016/j.cell.2011.08.024
[113] Zipperer, M. (2019) WHO Calls for an Immediate Halt to Provision of Single-Drug Artemisinin Malaria Pills.
[114] Chung, V.C.H., Wu, X., Hui, E.P., et al. (2015) Effectiveness of Chinese Herbal Medicine for Cancer Palliative Care: Overview of Systematic Reviews with Me- ta-Analyses. Scientific Reports, 5, Article No. 18111. https://doi.org/10.1038/srep18111
[115] Zhao, X., Zhu, Y., Hu, J., et al. (2018) Shikonin Inhibits Tumor Growth in Mice by Suppressing Pyruvate Kinase M2-Mediated Aerobic Glycolysis. Scientific Reports, 8, Article No. 14517. https://doi.org/10.1038/s41598-018-31615-y
[116] Chen, J., Xie, J., Jiang, Z., et al. (2011) Shikonin and Its Analogs Inhibit Cancer Cell Glycolysis by Targeting Tumor Pyruvate Kinase-M2. Oncogene, 30, 4297-4306. https://doi.org/10.1038/onc.2011.137
[117] James, A.D., Richardson, D.A., Oh, I.W., et al. (2020) Cutting off the Fuel Supply to Calcium Pumps in Pancreatic Cancer Cells: Role of Pyruvate Kinase-M2 (PKM2). British Journal of Cancer, 122, 266-278. https://doi.org/10.1038/s41416-019-0675-3
[118] Shilnikova, K., Piao, M.J., Kang, K.A., et al. (2018) Shikonin Induces Mitochondria-Mediated Apoptosis and Attenuates Epithelial-Mesenchymal Transition in Cisplatin-Resistant Human Ovarian Cancer Cells. Oncology Letter, 15, 5417-5424. https://doi.org/10.3892/ol.2018.8065
[119] Zhang, H. and Tsao, R. (2016) Dietary Polyphenols, Oxidative Stress and Antioxidant and Anti-Inflammatory Effects. Current Opinion in Food Science, 8, 33-42. https://doi.org/10.1016/j.cofs.2016.02.002
[120] (2013) The COVID-19 Outbreak Is an Emerging, Rapidly Evolving Situation. https://nccih.nih.gov/health/antioxidants/introduction.htm
[121] Zhou, Y., Zheng, J., Li, Y., Xu, D.P., Li, S., Chen, Y.M., et al. (2016) Natural Poly- phenols for Prevention and Treatment of Cancer. Nutrients, 8, 515. https://doi.org/10.3390/nu8080515
[122] Fujiki, H., Sueoka, E., Watanabe, T. and Suganuma, M. (2015) Primary Cancer Prevention by Green Tea, and Tertiary Cancer Prevention by the Combination of Green Tea Catechins and Anticancer Compounds. Journal of Cancer Prevention, 20, 1-4. https://doi.org/10.15430/JCP.2015.20.1.1
[123] Singh, K., Bhori, M., Kasu, Y.A., et al. (2018) Antioxidants as Precision Weapons in War against Cancer Chemotherapy Induced Toxicity-Exploring the Armoury of Obscurity. Saudi Pharmaceutical Journal, 26, 177-190. https://doi.org/10.1016/j.jsps.2017.12.013
[124] Stevenson, D.E. (2012) Polyphenols as Adaptogens—The Real Mechanism of the Antioxidant Effect? In: Rasooli, I., Ed., Bioactive Compounds in Phytomedicine, InTechOpen, London, 143-162. http://www.intechopen.com/books/bioactive-compounds-in-phytomedicine/polyph enols-as-adaptogensthe-real-mechanism-of-the-antioxidant-effect
[125] Warburg, O. (1996) Oxygen, the Creator of Differentiation, Biochemical Energetics. In: The Prime Cause and Prevention of Cancer, Academic Press, New York.
[126] Warburg, O. (1956) On the Origin of Cancer Cells. Science, 123, 309-314. https://doi.org/10.1126/science.123.3191.309
[127] Schulz, T.J., Thierbach, R., Voigt, A., et al. (2006) Induction of Oxidative Metabolism by Mitochondrial Frataxin Inhibits Cancer Growth. The Journal of Biological Chemistry, 281, 977-981. https://doi.org/10.1074/jbc.M511064200
[128] Miles, K.A. and Williams, R.E. (2008) Warburg Revisited: Imaging Tumor Blood Flow and Metabolism. Cancer Imaging, 8, 81-86. https://doi.org/10.1102/1470-7330.2008.0011
[129] Heiden, M.G.V., Cantley, L.C. and Thompson, C.B. (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science, 324, 1029-1033. https://doi.org/10.1126/science.1160809
[130] Garber, K. (2004) Energy Boost: The Warburg Effect Returns in a New Theory of Cancer. JNCI: Journal of the National Cancer Institute, 96, 1805-1806. https://doi.org/10.1093/jnci/96.24.1805
[131] Seyfried, T.N. and Mukherjee, P. (2005) Targeting Energy Metabolism in Brain Cancer: Review and Hypothesis. Nutrition & Metabolism, 2, 30-38. https://doi.org/10.1186/1743-7075-2-30
[132] Xiaolong, M. and Riordan, N.H. (2006) Cancer Is a Functional Repair Tissue. Medical Hypotheses, 66, 486-490. https://doi.org/10.1016/j.mehy.2005.09.041
[133] Wardman, P. (2001) Electron Transfer and Oxidative Stress as Key Factors in the Design of Drug Selectively Active in Hypoxia. Current Medicinal Chemistry, 8, 739-761. https://doi.org/10.2174/0929867013372959

[134] Tracy, K., Dibling, B.C., Spike, B.T., Knabb, J.R., Schumacker, P. and MacLeod, K.F. (2007) BNIP3 Is an RB/E2F Target Gene Required for Hypoxia-Induced Autophagy. Molecular and Cellular Biology, 27, 6229-6242. https://doi.org/10.1128/MCB.02246-06
[135] Al-Mehdi, A.B., Pastukh, V.M., Swiger, B.M., Reed, D.J., Patel, M.R., Bardwell, G.C., et al. (2012) Perinuclear Mitochondrial Clustering Creates Antioxidant-Rich Nuclear Domain Required for Hypoxia-Induced Transcription. Science Signaling, 5, ra47. https://doi.org/10.1126/scisignal.2002712
[136] Boland, M.L., Chourasia, A.H. and Macleod, K.F. (2013) Mitochondrial Dysfunction in Cancer. Frontiers in Oncology, 3, Article No. 292. https://doi.org/10.3389/fonc.2013.00292
[137] Wallace, D.C. (2005) Mitochondria and Cancer: Warburg Addressed. Cold Spring Harbour Symposia on Quantitative Biology, 70, 636-649. https://doi.org/10.1101/sqb.2005.70.035
[138] Schavemaker, P.E., Boersma, A.J. and Poolman, B. (2018) How Important Is Protein Diffusion in Prokaryotes? Frontiers in Molecular Biosciences, 5, Article No. 293. https://doi.org/10.3389/fmolb.2018.00093
[139] Wright, G.D. (2007) On the Road to Bacterial Cell Death. Cell, 130, 781-783. https://doi.org/10.1016/j.cell.2007.08.023
[140] Petrelli, F., Ghidini, M., Ghidini, A., et al. (2019) Use of Antibiotics and Risk of Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Cancers, 11, Article 1174. https://doi.org/10.3390/cancers11081174
[141] Kim, H., Lee, J.E., Hong, S.H., et al. (2019) The Effect of Antibiotics on the Clinical Outcomes of Patients with Solid Cancer Undergoing Immune Checkpoint Inhibitor Treatment: A Retrospective Study. BMC Cancer, 19, Article No. 21100. https://doi.org/10.1186/s12885-019-6267-z
[142] McKee, A., Hall, L.J. and Robinson, S.D. (2019) The Microbiota, Antibiotics and Breast Cancer. Breast Cancer Management, 8, BMT29. https://doi.org/10.2217/bmt-2019-0015
[143] Bordonaro, M. (2018) Hypothesis: Cancer Is a Disease of Evolved Trade-Offs between Neoplastic Virulence and Transmission. Journal of Cancer, 9, 1707-1724. https://doi.org/10.7150/jca.24679
[144] Medicinal Mushrooms (PDQ®)-Health Professional Version. https://www.cancer.gov/about-cancer/treatment/cam/hp/mushrooms-pdq
[145] Wasser, S.P. (2014) Medicinal Mushroom Science: Current Perspectives, Advances, Evidences, and Challenges. Biomedical Journal, 37, 345-356. https://doi.org/10.4103/2319-4170.138318
[146] Ng, T.B. (1998) A Review of Research on the Protein-Bound Polysaccharide (Polysaccharopeptide, PSP) from the Mushroom Coriolus Versicolor (Basidiomycetes: Polyporaceae). General Pharmacology, 30, 1-4. https://doi.org/10.1016/S0306-3623(97)00076-1
[147] Konno, S. (2009) Synergistic Potentiation of D-Fraction with Vitamin C as Possible Alternative Approach for Cancer Therapy. International Journal of General Medi- cine, 2, 91-108. https://doi.org/10.2147/IJGM.S5498
[148] Masuda, Y., Inoue, H., Ohta, H., et al. (2013) Oral Administration of Soluble B-Glucans Extracted from Grifola Frondosa Induces Systemic Antitumor Immune Response and Decreases Immunosuppression in Tumor-Bearing Mice. International Journal of Cancer, 133, 108-120. https://doi.org/10.1002/ijc.27999
[149] Shomori, K., Yamamoto, M., Arifuku, I., Teramachi, K. and Ito, H. (2009) Antitumor Effects of a Water-Soluble Extract from Maitake (Grifola frondosa) on Human Gastric Cancer Cell Lines. Oncology Reports, 22, 615-620. https://doi.org/10.3892/or_00000480
[150] Masuda, Y., Murata, Y., Hayashi, M. and Nanba, H. (2008) Inhibitory Effect of Mdfraction on Tumor Metastasis: Involvement of NK Cell activation and Suppression of Intercellular Adhesion Molecule (ICAM)-1 Expression in Lung Vascular Endothelial Cells. Biological and Pharmaceutical Bulletin, 31, 1104-1108. https://doi.org/10.1248/bpb.31.1104
[151] Masuda, Y., Nakayama, Y., Tanaka, A., Naito, K. and Konishi, M. (2017) Antitumor Activity of Orally Administered Maitake A-Glucan by Stimulating Antitumor Immune Response in Murine Tumor. PLOS ONE, 12, e0173621. https://doi.org/10.1371/journal.pone.0173621
[152] Zhao, F., Zhao, J., Song, L., Zhang, Y.Q., Guo, Z. and Yang, K.H. (2017) The Induction of Apoptosis and Autophagy in Human Hepatoma SMMC-7721 Cells by Combined Treatment with Vitamin C and Polysaccharides Extracted from Grifola Frondosa. Apoptosis, 22, 1461-1472. https://doi.org/10.1007/s10495-017-1421-z
[153] Lin, H., She Y.-H., Cassileth, B.R. et al. (2004) Maitake Beta-Glucan MD-Fraction Enhances Bone Marrow Colony Formation and Reduces Doxorubicin Toxicity in Vitro. International Immunopharmacology, 4, 91-99. https://doi.org/10.1016/j.intimp.2003.10.012
[154] Dai, X., Stanilka, J.M., Rowe, C.A., Esteves, E.A., et al. (2015) Consuming Lentinula Edodes (Shiitake) Mushrooms Daily Improves Human Immunity: A Randomized Dietary Intervention in Healthy Young Adults. Journal of the American College of Nutrition, 34, 478-487. https://doi.org/10.1080/07315724.2014.950391

[155] Ina, K., Furuta, R., Kataoka, T., et al. (2016) Chemo-Immunotherapy Using Lentinan for the Treatment of Gastrick Cancer with Liver Metastases. Medical Sciences, 4, Article 8. https://doi.org/10.3390/medsci4020008
[156] Rincão, V.P., Yamamoto, K.A., Ricardo, N.M., et al. (2012) Polysaccharide and Extracts from Lentinula Edodes: Structural Features and Antiviral Activity. Virology Journal, 9, Article No. 37. https://doi.org/10.1186/1743-422X-9-37
[157] Kim, S.P., Park, S.O., Lee, S.J., Nam, S.H. and Friedman, M. (2014) A Polysaccharide Isolated from the Liquid Culture of Lentinus Edodes (Shiitake) Mushroom Mycelia Containing Black Rice Bran Protects Mice against Salmonellosis through Upregulation of the Th1 Immune Reaction. Journal of Agricultural and Food Chemistry, 62, 2384-2391. https://doi.org/10.1021/jf405223q
[158] Tanigawa, K., Itoh, Y. and Kobayashi, Y. (2016) Improvement of QOL and Immunological Function with Lentinula Edodes Mycelia in Patients Undergoing Cancer Immunotherapy: An Open Pilot Study. Alternative Therapies in Health and Medi- cine, 22, 36-42.
[159] Jin, X., Ruiz, B.J., Sze, D.M.Y. and Chan, G.C.F. (2016) Ganoderma Lucidum (Reishi Mushroom) for Cancer Treatment (Review). Cochrane Database of Systematic Reviews, No. 4, CD007731. https://doi.org/10.1002/14651858.CD007731.pub3
[160] Wang, C., Shi, S., Chen, Q., et al. (2018) Antitumor and Immunomodulatory Activities of Ganoderma lucidum Polysaccharides in Glioma-Bearing Rats. Integrative Cancer Therapies, 17, 674-683. https://doi.org/10.1177/1534735418762537
[161] Gill, S.K. and Rieder, M.J. (2008) Toxicity of a Traditional Chinese Medicine, Ganoderma lucidum, in Children with Cancer. Canadian Journal of Clinical Pharmacology, 15, e275-e285.
[162] Yuen, M.F., Ip, P., Ng, W.K. and Lai, C.L. (2004) Hepatotoxicity Due to a Formulation of Ganoderma lucidum (Lingzhi). Journal of Hepatology, 41, 686-687. https://doi.org/10.1016/j.jhep.2004.06.016
[163] Wanmuang, H., Leopairut, J., Kositchaiwat, C., Wananukul, W. and Bunyaratvej, S. (2007) Fatal Fulminant Hepatitis Associated with Ganoderma lucidum (Lingzhi) Mushroom Powder. Journal of the Medical Association of Thailand, 90, 179-181.
[164] Bhushan, A. and Kulshreshtha, M. (2018) The Medicinal Mushroom Agaricus Bisporus: Review of Phytopharmacology and Potential Role in the Treatment of Various Diseases. Journal of Nature and Science of Medicine, 1, 4-9.
[165] Vetter, J. (2003) Chemical Composition of Fresh Conserved Agaricus bisporus Mushroom. European Food Research and Technology, 217, 10-12. https://doi.org/10.1007/s00217-003-0707-2
[166] Firenzuoli, F., Gori, L. and Lombardo, G. (2007) The Medicinal Mushroom Agaricus Blazei Murrill: Review of Literature and Pharmaco-Toxicological Problems. eCAM, 5, 3-15. https://doi.org/10.1093/ecam/nem007
[167] Piska, K., Muszynska, B. and Ziaja, K. (2017) Edible Mushroom Pleurotus ostreatus (Oyster Mushroom)—Its Dietary Significance and Biological Activity. Acta Scientiarum Polonorum Hortorum Cultus, 16, 151-161.
[168] Blagodatski, A., Yatsunskaya, M., Mikhailova, V., et al. (2018) Medicinal Mu- shrooms as an Attractive New Source of Natural Compounds for Future Cancer Therapy. Oncotarget, 9, 29259-29274. https://doi.org/10.18632/oncotarget.25660
[169] Xu, T., Beelman, R.B. and Lambert, J.D. (2012) The Cancer Preventive Effects of Edible Mushrooms. Anti-Cancer Agents in Medicinal Chemistry, 12, 1255-1263. https://doi.org/10.2174/187152012803833017
[170] Horneber, M.A., Bueschel, G., Huber, R., et al. (2008) Mistletoe Therapy in Oncology. Cochrane Database of Systematic Reviews, No. 2, CD003297. https://doi.org/10.1002/14651858.CD002833.pub2
[171] Ostermann, T., Raak, C. and Bussing, A. (2009) Survival of Cancer Patients Treated With Mistletoe Extract (Iscador): A Systematic Literature Review. BMC Cancer, 9, Article No. 451. https://doi.org/10.1186/1471-2407-9-451
[172] Melzer, J., Iten, F., Hostanska, K., et al. (2009) Efficacy and Safety of Mistletoe Preparations (Viscum album) for Patients with Cancer Diseases. A Systematic Re- view. Forschende Komplementärmedizin, 16, 217-226. https://doi.org/10.1159/000226249
[173] Kleijnen, J. and Knipschild, P. (1994) Mistletoe Treatment for Cancer Review of Controlled Trials in Humans. Phytomedicine, 1, 255-260. https://doi.org/10.1016/S0944-7113(11)80073-5
[174] Lyu, S.Y. and Park, W.B. (2007) Effects of Korean Mistletoe Lectin (Viscum album Coloratum) on Proliferation and Cytokine Expression in Human Peripheral Blood Mononuclear Cells and T-Lymphocytes. Archives of Pharmacal Research, 30, 1252-1264. https://doi.org/10.1007/BF02980266
[175] Witters, L.A. (2001) The Blooming of the French Lilac. The Journal of Clinical Investigation, 108, 1105-1107. https://doi.org/10.1172/JCI14178
[176] Werner, E. and Bell, J. (1922). The Preparation of Methylguanidine, and of Bβ-Dimethylguanidine by the Interaction of Dicyandiamide, and Methylammonium and Dimethylammonium Chlorides

Respectively. Journal of the Chemical Society, Transactions, 121, 1790-1795. https://doi.org/10.1039/CT9222101790
[177] Zi, F., Zi, H., Li, Y., et al. (2018) Metformin and Cancer: An Existing Drug for Cancer Prevention and Therapy (Review). Oncology Letters, 15, 683-690. https://doi.org/10.3892/ol.2017.7412
[178] Gonzalez-Aungulo, A.M. and Meric-Bernstam, F. (2010) Metformin: A Therapeutic Opportunity in Breast Cancer. Clinical Cancer Research, 16, 1695-1700. https://doi.org/10.1158/1078-0432.CCR-09-1805
[179] Li, C., Xue, Y., Xi, Y.R. and Xie, K. (2017) Progress in the Application and Mechanism of Metformin in Treating Non-Small Cell Lung Cancer (Review). Oncology Letters, 13, 2873-2880. https://doi.org/10.3892/ol.2017.5862
[180] Rosilio, C., Ben-Sahra, I., Bost, F. and Peyron, J.F. (2014) Metformin: A Metabolic Disruptor and Anti-Diabetic Drug to Target Human Leukemia. Cancer Letters, 246, 188-196. https://doi.org/10.1016/j.canlet.2014.01.006
[181] Andrzejewski, S., Gravel, S.P., Pollak, M. and St-Pierre, J. (2014) Metformin Directly Acts on Mitochondria to Alter Cellular Bioenergetics. Cancer and Metabolism, 2, Article No. 12. https://doi.org/10.1186/2049-3002-2-12
[182] Devasagayam, T.P., Tilak, J.C., Boloor, K.K., Sane, K.S., Ghaskadbi, S.S. and Lele, R.D. (2004) Free Radicals and Antioxidants in Human Health: Current Status and Future Prospects. The Journal of the Association of Physicians of India, 52, 794-804.
[183] Sing, K., Bhori, M., Kasu, Y.A., et al. (2018) Antioxidants as Precision Weapons in War against Cancer Chemotherapy Induced Toxicity—Exploring the Armoury of Obscurity. Saudy Pharmaceutical Journal, 26, 177-190. https://doi.org/10.1016/j.jsps.2017.12.013
[184] Masri, O.A., Chalhoub, J.M. and Sharara, A.I. (2015) Role of Vitamins in Gastrointestinal Diseases. World Journal of Gastroenterology, 21, 5191-5209. https://doi.org/10.3748/wjg.v21.i17.5191
[185] Funk, C. (1912) The Etiology of the Deficiency Diseases. Journal of State Medicine, 20, 341-368.
[186] Piro, A., Tagarelli, G., Lagonia, P., et al. (2010) Casimir Funk: His Discovery of the Vitamins and Their Deficiency Disorders. Annals of Nutrition and Metabolism, 57, 85-88. https://doi.org/10.1159/000319165
[187] Thyagarajan, A. and Sahu, R.P. (2018) Potential Contributions of Antioxidants to Cancer Therapy: Immunomodulation and Radiosensitization. Integrative Cancer Therapies, 17, 210-216. https://doi.org/10.1177/1534735416681639
[188] Antioxidants: In Depth. https://nccih.nih.gov/health/antioxidants/introduction.htm
[189] SzentGyörgyi, A. (1937) Oxidation, Energy Transfer, and Vitamins. Nobel Lecture.
[190] Stahelin, H.B. (1988) Vitamins and Cancer, Recent Results. In: Senn, H.J., Glaus, A. and Schmid, L., Eds., Supportive Care in Cancer Patients. Recent Results in Cancer Research, Vol. 108, Springer-Verlag, Berlin, 227-234. https://doi.org/10.1007/978-3-642-82932-1_28
[191] Cameron, E., Pauling, L. (1974) The Orthomolecular Treatment of Cancer. I. The Role of Ascorbic Acid in Host Resistance. Chemico-Biological Interactions, 9, 273-283. https://doi.org/10.1016/0009-2797(74)90018-0
[192] Cameron, E. and Pauling, L. (1976) Supplemental Ascorbate in the Supportive Treatment of Cancer: Prolongation of Survival Times in Terminal Human Cancer. Proceedings of the National Academy of Sciences of the United States of America, 73, 3685-3689. https://doi.org/10.1073/pnas.73.10.3685
[193] Cameron, E. and Campbell, A. (1991) Innovation vs. Quality Control: An "Unpublishable" Clinical Trial of Supplemental Ascorbate in Incurable Cancer. Medical Hypotheses, 36, 185-189. https://doi.org/10.1016/0306-9877(91)90127-K
[194] Cameron, E. and Pauling, L. (1978) Supplemental Ascorbate in the Supportive Treatment of Cancer: Reevaluation of Prolongation of Survival Times in Terminal Human Cancer. Proceedings of the National Academy of Sciences of the United States of America, 75, 4538-4542. https://doi.org/10.1073/pnas.75.9.4538
[195] Creagan, E.T., Moertel, C.G., O'Fallon, J.R., et al. (1979) Failure of High-Dose Vitamin C (Ascorbic Acid) Therapy to Benefit Patients with Advanced Cancer. A Controlled Trial. New England Journal of Medicine, 301, 687-690. https://doi.org/10.1056/NEJM197909273011303
[196] Tschetter, L., et al. (1983) A Community-Based Study of Vitamin C (Ascorbic Acid) in Patients with Advanced Cancer. Proceedings of the American Society of Clinical Oncology, 2, Article No. 92.
[197] Shenoy, N., Creagan, E., Witzig, T. and Levine, M. (2018) Ascorbic Acid in Cancer Treatment: Let the Phoenix Fly. Cancer Cell, 34, 700-706. https://doi.org/10.1016/j.ccell.2018.07.014
[198] Reczek, C.R. and Chandel, N.S. (2015) Revisiting Vitamin C and Cancer. Science, 350, 1317-1318. https://doi.org/10.1126/science.aad8671
[199] Hoffer, L.J., Levine, M., Assouline, S., et al. (2008) Phase I Clinical Trial of I.V. Ascorbic Acid in Advanced Malignancy. Annals of Oncology, 19, 1969-1974. https://doi.org/10.1093/annonc/mdn377

[200] Stephenson, C.M., Levin, R.D., Spector, T., et al. (2013) Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of High-Dose Intravenous Ascorbic Acid in Patients with Advanced Cancer. Cancer Chemotherapy and Pharmacology, 72, 139-146. https://doi.org/10.1007/s00280-013-2179-9
[201] Riordan, H.D., Casciari, J.J., Gonzalez, M.J., et al. (2005) A Pilot Clinical Study of Continuous Intravenous Ascorbate in Terminal Cancer Patients. Puerto Rico Health Sciences Journal, 24, 269-276.
[202] Carr, A.C., Vissers, M.C.M. and Cook, J. (2014) Relief from Cancer Chemotherapy Side Effects with Pharmacologic Vitamin C. New Zealand Medical Journal, 127, 66-70.
[203] Ma, Y., Chapman, J., Levine, M., Polireddy, K., Drisko, J. and Chen, Q. (2014) High-Dose Parenteral Ascorbate Enhanced Chemosensitivity of Ovarian Cancer and Reduced Toxicity of Chemotherapy. Science Translational Medicine, 6, 222-218. https://doi.org/10.1126/scitranslmed.3007154
[204] Monti, D.A., Mitchell, E., Bazzan, A.J., Littman, S., Zabrecky, G., Yeo, C.J., Pillai, M.V., Newberg, A.B., Deshmukh, S. and Levine, M. (2012) Phase I Evaluation of Intravenous Ascorbic Acid in Combination with Gemcitabine and Erlotinib in Patients with Metastatic Pancreatic Cancer. PLOS ONE, 7, e29794. https://doi.org/10.1371/journal.pone.0029794
[205] Welsh, J.L., Wagner, B.A., van't Erve, T.J., et al. (2013) Pharmacological Ascorbate with Gemcitabine for the Control of Metastatic and Node-Positive Pancreatic Cancer (PACMAN): Results from a Phase I Clinical Trial. Cancer Chemotherapy and Pharmacology, 71, 765-775. https://doi.org/10.1007/s00280-013-2070-8
[206] Ou, J., Zhu, X., Lu, Y., et al. (2017) The Safety and Pharmacokinetics of High Dose Intravenous Ascorbic Acid Synergy with Modulated Electrohyperthermia in Chinese Patients with Stage III-IV Non-Small Cell Lung Cancer. European Journal of Pharmaceutical Sciences, 109, 412-418. https://doi.org/10.1016/j.ejps.2017.08.011
[207] Carr, A.C., Vissers, M.C.M. and Cook, J. (2014) The Effect of Intravenous Vitamin C on Cancer—And Chemotherapy-Related Fatigue and Quality of Life. Frontiers in Oncology, 4, Article No. 283. https://doi.org/10.3389/fonc.2014.00283
[208] Vollbracht, C., Schneider, B., Leendert, V., Weiss, G., Auerbach, L. and Beuth, J. (2011) Intravenous Vitamin C Administration Improves Quality of Life in Breast Cancer Patients during Chemo-/Radiotherapy and Aftercare: Results of a Retrospective, Multicentre. Epidemiological Cohort Study in Germany, in Vivo, 25, 983-990.
[209] Da Mata, A.M.O.F., De Carvalho, R.M., De Alencar, M.V.O.B., Cavalcante, A.M.D.C.M. and Da Silva, B.B. (2016) Ascorbic Acid in the Prevention and Treatment of Cancer. Revista da Associação Médica Brasileira, 62, 680-686. https://doi.org/10.1590/1806-9282.62.07.680
[210] Mikirova, N., Casciari, J., Rogers, A. and Taylor, P. (2012) Effect of High-Dose Intravenous Vitamin C on Inflammation in Cancer Patients. Journal of Translational Medicine, 10, Article No. 189. https://doi.org/10.1186/1479-5876-10-189
[211] Barrett, S. (2011, October 3) High Doses of Vitamin C Are Not Effective as a Cancer Treatment. https://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/c.html
[212] Vissers, M.C.M. and Das, A.B. (2018) Potential Mechanisms of Action for Vitamin C in Cancer: Reviewing the Evidence. Frontiers in Physiology, 9, Article No. 809. https://doi.org/10.3389/fphys.2018.00809
[213] Bast, A. and Haenen, G.R.M.M. (2013) Ten Misconceptions about Antioxidants. Trends in Pharmacological Sciences, 34, 430-436. https://doi.org/10.1016/j.tips.2013.05.010
[214] Podmore, I.D., Griffiths, H.R., Herbert, K.E., et al. (1998) Vitamin C Exhibits Pro-Oxidant Properties. Nature, 392, Article No.559. https://doi.org/10.1038/33308
[215] Myung, S.K. and Yang, H.J. (2013) Efficacy of Vitamin and Antioxidant Supple- ments in Prevention of Esophageal Cancer: Meta-Analysis of Randomized Controlled Trials. Journal of Cancer Prevention, 18, 135-143. https://doi.org/10.15430/JCP.2013.18.2.135
[216] Jain, A., Tiwari, A., Verma, A., et al. (2017) Vitamins for Cancer Prevention and Treatment: An Insight. Current Molecular Medicine, 17, 321-340. https://doi.org/10.2174/1566524018666171205113329
[217] Mut-Salud, N., Álvarez, P.J., Garrido, J.M., et al. (2016) Antioxidant Intake and Antitumor Therapy: Toward Nutritional Recommendations for Optimal Results. Oxidative Medicine and Cellular Longevity, 2016, Article ID: 6719534. https://doi.org/10.1155/2016/6719534
[218] Watson, J. (2013) Oxidants, Antioxidants and the Current Incurability of Metastatic Cancers. Open Biology, 3, Article ID: 120144. https://doi.org/10.1098/rsob.120144
[219] (2013) James Watson Hypothesis Links Cancer to Antioxidants. https://www.genengnews.com/topics/omics/james-watson-hypothesis-links-cancer- to-antioxidants
[220] Meffert, H. (2008) Antioxidants—Friend or Foe? GMS German Medical Science, 6, Doc09. https://www.egms.de/static/en/journals/gms/2008-6/000054.shtml

[221] Bjelakovic, G., Nikolova, D., et al. (2007) Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-Analysis. JAMA, 297, 842-857. https://doi.org/10.1001/jama.297.8.842
[222] Bjelakovic, G., Nikolova, D., Gluud, L.L., et al. (2007) Review: Antioxidant Supplements for Primary and Secondary Prevention Do Not Decrease Mortality. JAMA, 297, 842-857. https://doi.org/10.1001/jama.297.8.842
[223] Bjelakovic, G., Nikolova, D. and Gluud, C. (2013) Meta-Regression Analyses, Me- ta-Analyses, and Trial Sequential Analyses of the Effects of Supplementation with Be- ta-Carotene, Vitamin A, and Vitamin E Singly or in Different Combinations on All-Cause Mortality: Do We Have Evidence for Lack of Harm? PLOS ONE, 8, e74558. https://doi.org/10.1371/journal.pone.0074558
[224] Bjelakovic, G., Nikolova, D. and Simonetti, R.G. (2008) Systematic Review—Primary and Secondary Prevention of Gastrointestinal Cancers with Antioxidant Supplements. Alimentary Pharmacology & Therapeutics, 28, 689-703. https://doi.org/10.1111/j.1365-2036.2008.03785.x
[225] Dotan, Y., Pinchuk, I., Lichtenberg, D., et al. (2009) Decision Analysis Supports the Paradigm That Indiscriminate Supplementation of Vitamin E Does More Harm than Good. Arteriosclerosis, Thrombosis, and Vascular Biology, 29, 1304-1309. https://doi.org/10.1161/ATVBAHA.108.178699
[226] Akanji, M.A., Fatinukun, H.D. and Rotini, D.E. (2020) The Two Sides of Dietary Antioxidants in Cancer Therapy. InTech Open, 1-16. https://www.intechopen.com/chapters/66504
[227] Acharya, A., Das, I., Chandhok, D. and Saha, T. (2010) Redox Regulation in Cancer: A Double-Edged Sword with Therapeutic Potential. Oxidative Medicine and Cellular Longevity, 3, 23-34. https://doi.org/10.4161/oxim.3.1.10095
[228] Aasdi-Samani, M., Farkhad, N.K., Mahmoudian-Sani, M.R., et al. (2019) Antioxidants as a Double-Edged Sword in the Treatment of Cancer. In: Shalaby, E., Ed., Antioxidants, IntechOpen, London. https://www.intechopen.com/chapters/66504
[229] Conklin, K.A. (2004) Cancer Chemotherapy and Antioxidants. The Journal of Nutrition, 134, 3201S-3204S. https://doi.org/10.1093/jn/134.11.3201S
[230] Sznarkowska, A., Kostecka, A., Meller, K. and Bielawski, K.P. (2017) Inhibition of Cancer Antioxidant Defense by Natural Compounds. Oncotarget, 8, 15996-16016. https://doi.org/10.18632/oncotarget.13723
[231] Szasz, O., Szigeti, G.P. and Szasz, A. (2017) On the Self-Similarity in Biologyical Processes. OJBIPHY, 7, 183-196. https://doi.org/10.4236/ojbiphy.2017.74014
[232] Szasz, O., Szigeti, G.P. and Szasz, A. (2019) The Intrinsic Self-Time of Biosystems. OJBIPHY, 9, 131-145.
[233] Kovacic, P. and Osuna, J.A. (2000) Mechanisms of Anti-Cancer Agents: Emphasis on Oxidative Stress and Electron Transfer. Current Pharmaceutical Design, 6, 277-309. https://doi.org/10.2174/1381612003401046
[234] Mamede, A.C., Tavares, S.D., Abrantes, A.M., et al. (2011) Role of Vitamins in Cancer: A Review. Nutrition and Cancer, 63, 479-494. https://doi.org/10.1080/01635581.2011.539315
[235] Teitelbaum, H.A. (1956) Homeostasis and Personality. Archives of Neurology & Psychiatry, 76, 317-324. https://doi.org/10.1001/archneurpsyc.1956.02330270089016
[236] Stagner, R. (1951) Homeostasis as a Unifying Concept in Personality Theory. Psychological Review, 58, 5-17. https://doi.org/10.1037/h0063598
[237] Cummins, R.A., Gullone, E. and Lau, A.L.D. (2002) A Model of Subjective Well-Being Homeostasis: The Role of Personality. In: Gullone, E. and Cummins, R.A., Eds., The Universality of Subjective Wellbeing Indicators, Social Indicators Research Series, Vol. 16, Springer, Dordrecht, 7-46. https://doi.org/10.1007/978-94-010-0271-4
[238] Dicks, L.M.T., Geldenhuys, J., Mikkelsen, L.S., et al. (2018) Our Gut Microbiota: A Long Walk to Homeostasis. Benef Microbes, 9, 3-20. https://doi.org/10.3920/BM2017.0066
[239] Pédron, T., Nigro, G. and Sansonetti, P.J. (2016) From Homeostasis to Pathology: Decrypting Microbe-Host Symbiotic Signals in the Intestinal Crypt. Philosophical Transactions of the Royal Society B, 371, Article ID: 20150500. https://doi.org/10.1098/rstb.2015.0500
[240] Armour, C.R., Nayfach, S., Pollard, K.S. and Sharpton, T.J. (2019) A Metagenomic Meta-Analysis Reveals Functional Signatures of Health and Disease in the Human Gut Microbiome. mSystems, 4, e00332-18. https://doi.org/10.1128/mSystems.00332-18
[241] Huybrechts, I., Zouiouich, S., Loobuyck, A., et al. (2020) The Human Microbiome in Relation to Cancer Risk: A Systematic Review of Epidemiologic Studies. Cancer Epidemiology, Biomarkers & Prevention, 10, 1856-1868. https://doi.org/10.1158/1055-9965.EPI-20-0288
[242] Gethings-Behncke, C., Coleman, H.G., Jordao, H.W.T., et al. (2020) Fusobacterium nucleatum in the Colorectum and Its Association with Cancer Risk and Survival: A Systematic Review and Meta-Analysis. Cancer Epidemiology, Biomarkers & Prevention, 3, 539-548. https://doi.org/10.1158/1055-9965.EPI-18-1295

[243] Brusselaers, N., Shrestha, S., van de Wijgert, J. and Verstraelen, H. (2019) Vaginal Dysbiosis and the Risk of Human Papillomavirus and Cervical Cancer: Systematic Review and Meta-Analysis. American Journal of Obstetrics and Gynecology, 221, 9-18.e8. https://doi.org/10.1016/j.ajog.2018.12.011
[244] Yang, J.J., Yu, D., Xiang, Y.B., et al. (2020) Association of Dietary Fiber and Yogurt Consumption with Lung Cancer Risk: A Pooled Analysis. JAMA Oncology, 6, e194107. https://doi.org/10.1001/jamaoncol.2019.4107
[245] Perrone, A.M., Pirovano, C., Borghese, G., et al. (2019) Palliative Electrochemotherapy in Vulvar Carcinoma: Preliminary Results of the ELECHTRA (Electrochemotherapy Vulvar Cancer) Multicenter Study. Cancers, 11, 657. https://doi.org/10.3390/cancers11050657
[246] Mazzocca, A. (2019) The Systemic-Evolutionary Theory of the Origin of Cancer (SETOC): A New Interpretative Model of Cancer as a Complex Biological System. International Journal of Molecular Sciences, 20, Article 4885. https://doi.org/10.3390/ijms20194885
[247] Sharma, V. (2016) The Application of Chaos Theory and Fractal Mathematics to the Study of Cancer Evolution: Placing Metabolism and Immunity Centre Stage. Medical Research Archives, 4, 1-12. https://doi.org/10.18103/mra.v4i6.717
[248] Balmain, A., Gray, J. and Ponder, B. (2014) The Genetics and Genomics of Cancer. Nature Genetics, 33, 238-244. https://doi.org/10.1038/ng1107
[249] Szigeti, G.P., Szasz, O. and Hegyi, G. (2017) Connections between Warburg's and Szentgyorgyi's Approach about the Causes of Cancer. Journal of Neoplasm, 1, Article No. 8. http://neoplasm.imedpub.com/connections-between-warburgs-and-szentgyorgyis-a pproach-about-thecauses-of-cancer.pdf
[250] Hanahan, D. and Weinberg, R.A. (2000) The Hallmarks of Cancer. Cell, 100, 57-70. https://doi.org/10.1016/S0092-8674(00)81683-9
[251] Dyas, F.G. (1928) Chronic Irritation as a Cause of Cancer. JAMA, 90, 457. https://doi.org/10.1001/jama.1928.92690330003008c
[252] Dvorak, H.F. (1986) Tumors: Wounds that Do Not Heal, Similarities between Tumor Stroma Generation and Wound Healing. The New England Journal of Medicine, 315, 1650-1659. https://doi.org/10.1056/NEJM198612253152606
[253] Platz, E.A. and De Marzo, A.M. (2004) Epidemiology of Inflammation and Prostate Cancer. The Journal of Urology, 171, S36-S40. https://doi.org/10.1097/01.ju.0000108131.43160.77
[254] Hanahan, D. and Weinberg, R.A. (2011) Hallmarks of Cancer: The Next Generation. Cell, 144, 646-674. https://doi.org/10.1016/j.cell.2011.02.013
[255] Punyiczki, M. and Fesus, L. (1998) Heat Shock and Apoptosis: The Two Defense Systems of the Organisms May Have Overlapping Molecular Elements. Annals of the New York Academy of Sciences, 951, 67-74. https://doi.org/10.1111/j.1749-6632.1998.tb08978.x
[256] Popkin, G. (2011) Physics Sheds Light on Cancer and Bacteria Evolution. APC News, Vol. 20, No. 5. https://www.aps.org/publications/apsnews/201105/cancerbacteria.cfm
[257] Trigos, A.S., Pearson, R.B., Paenfuss, A.T., et al. (2018) How the Evolution of Multicellularity Set the Stage for Cancer. British Journal of Cancer, 118, 145-152. https://doi.org/10.1038/bjc.2017.398
[258] Trigos, A.S., Pearson, R.B., Papenfuss, A.T., et al. (2016) Altered Interactions be- tween Unicellular and Multicellular Genes Drive Hallmarks of Transformation in a Diverse Range of Solid Tumors. PNAS, 114, 6406-6411. https://doi.org/10.1073/pnas.1617743114
[259] Aktipis, C.A., Bobby, A.M., Jansen, G., et al. (2015) Cancer across the Tree of Life: Cooperation and Cheating in Multicellularity. Philosophical Transactions of the Royal Society B, 370, Article ID: 20140219. https://doi.org/10.1098/rstb.2014.0219
[260] Davidson, C.D., Wang, W.Y., Zaimi, I., et al. (2019) Cell Force-Mediated Matrix Reorganization Underlies Multicellular Network Assembly. Scientific Reports, 9, Article No. 12. https://doi.org/10.1038/s41598-018-37044-1
[261] Jezequel, P. and Campone, M. (2018) Comment on "How the Evolution of Multi- cellularity Set the Stage for Cancer". British Journal of Cancer, 119, 133-134. https://doi.org/10.1038/s41416-018-0091-0
[262] Szentgyorgyi, A. (1998) Electronic Biology and Cancer. Marcel Dekker, New York.
[263] Kirson, E.D., Gurvich, Z., Schneiderman, R., et al. (2004) Disruption of Cancer Cell Replication by Alternating Electric Fields. Cancer Research, 64, 3288-3295. https://doi.org/10.1158/0008-5472.CAN-04-0083
[264] Vincze, G., Sziget, G.P. and Szasz, A. (2016) Reorganization of the Cytoskeleton. Journal of Advances in Biology, 9, 1872-1882. https://cirworld.com/index.php/jab/article/view/4059
[265] Springer, M. and Paulsson, J. (2006) Harmonies from Noise. Nature, 439, 27-28. https://doi.org/10.1038/439027a
[266] West, J.B. (2013) Fractal Physiology and Chaos in Medicine. World Scientific, Singapore. https://doi.org/10.1142/8577

[267] Szasz, O., Vincze, G., Szigeti, G.P. and Szasz, A. (2017) Intrinsic Noise Monitoring of Complex Systems. OJBIPHY, 7, 197-215. https://doi.org/10.4236/ojbiphy.2017.74015
[268] Friedman, E., Verderame, M., Winawer, S. and Pollack, R. (1984) Actin Cytoskeletal Organization Loss in the Benign-to-Malignant Tumor Transition in Cultured Human Colonic Epithelial Cells. Cancer Research, 44, 3040-3050.
[269] Suresh, S. (2007) Biomechanics and Biophysics of Cancer Cells. Acta Biomaterialia, 3, 413-438. https://doi.org/10.1016/j.actbio.2007.04.002
[270] Plodinec, M., Loparic, M., Monnier, C.A., et al. (2012) The Nanomechanical Signature of Breast Cancer. Nature Nanotechnology, 7, 757-765. http://www.nature.com/nnano/journal/v7/n11/full/nnano.2012.167.html?WT.ec_id=NNANO-201211
[271] Wirts, D., Konstantopoulos, K. and Searson, P.C. (2011) The Physics of Cancer: The Role of Physical Interactions and Mechanical Forces in Metastasis. Nature Reviews, Cancer, 11, 512-518. https://doi.org/10.1038/nrc3080
[272] Uklrich, T.A., Pardo, E.M.D.J. and Kumar, S. (2009) The Mechanical Rigidity of the Extracellular Matrix Regulates the Structure, Motility, and Proliferation of Glioma Cells. Cancer Research, 69, 4167-4175. https://doi.org/10.1158/0008-5472.CAN-08-4859
[273] Hameroff, S.R. (1988) Coherence in the Cytoskeleton: Implications for Biological Information Processing. In: Froelich, H., Ed., Biological Coherence and Response to External Stimuli, Springer Verlag, Berlin, 242-266. https://doi.org/10.1007/978-3-642-73309-3_14
[274] Janmey, P. (1995) Cell Membranes and the Cytoskeleton. In: Lipowsky, R. and Sackinan, E., Eds., Handbook of Biological Physics, Volume I, Elsevier Science, Amsterdam, 805-849. https://doi.org/10.1016/S1383-8121(06)80010-2
[275] Del, Giudice, E., et al. (1988) Structures, Correlations and Electroimagnetic Interactions in Living Matter. In: Froelich, H., Ed., Biological Coherence and Response to External Stimuli, Springer Verlag, Berlin, 49-64. https://doi.org/10.1007/978-3-642-73309-3_3
[276] Cho, M.R., Thatte, H.S., Lee, R.C., et al. (1996) Reorganization of Microfilament Structure Induced by Ac Electric Fields. FASEB Journal, 10, 1552-1558. https://doi.org/10.1096/fasebj.10.13.8940302
[277] Agmon, N. (1995) The Grotthuss Mechanism. Chemical Physics Letters, 244, 456-462. https://doi.org/10.1016/0009-2614(95)00905-J
[278] Markovitch, O. and Agmon, N. (2007) Structure and Energetics of the Hydronium Hhydration Shells. The Journal of Physical Chemistry A, 111, 2253-2256. https://doi.org/10.1021/jp068960g
[279] Jackson, M.D.B., Duran-Nebreda, S. and Bassel, G.W. (2017) Network-Based Approaches to Quantify Multicellular Development. Journal of the Royal Society Interface, 14, Article ID: 20170484. https://doi.org/10.1098/rsif.2017.0484
[280] Adami, C. (1995) Self-Organized Criticality in Living Systems. Physics Letters A, 203, 29-32. https://doi.org/10.1016/0375-9601(95)00372-A
[281] Seo, H., Kim, W., Lee, J., et al. (2013) Network-Based Approaches for Anticancer Therapy (Review). International Journal of Oncology, 43, 1737-1744. https://doi.org/10.3892/ijo.2013.2114
[282] Barabasi, A.L., Menichetti, G. and Loscalzo, J. (2019) The Unmapped Chemical Complexity of Our Diet. Nature Food, 1, 33-37. https://doi.org/10.1038/s43016-019-0005-1
[283] Albert, R. (2005) Scale-Free Networks in Cell Biology. Journal of Cell Science, 118, 4947-4957. https://doi.org/10.1242/jcs.02714
[284] Bak, P., Chen, K. and Creutz, M. (1989) Self-Organized Criticality in the “Game of Life”. Nature, 342, 780-782. https://doi.org/10.1038/342780a0
[285] Bak, P., Tang, C. and Wiesenfeld, K. (1987) Self-Organized Criticality: An Explanation of 1/f Noise. Physical Review Letters, 59, 381-384. https://doi.org/10.1103/PhysRevLett.59.381
[286] Szendro, P., Vincze, G. and Szasz, A. (2001) Pink Noise Behaviour of the Bio-Systems. European Biophysics Journal, 30, 227-231. http://www.ncbi.nlm.nih.gov/pubmed/11508842
[287] Szendro, P., Vincze, G. and Szasz, A. (2001) Bio-Response to White Noise Excitation. Electro- and Magnetobiology, 20, 215-229. http://www.tandfonline.com/doi/abs/10.1081/JBC-100104145?journalCode=iebm19
[288] Szasz, A. (2014) Oncothermia: Complex Therapy by EM and Fractal Physiology. 31th URSI General Assembly and Scientific Symposium (URSI GASS), Beijing, 16-23 August 2014, 1-4. https://ieeexplore.ieee.org/document/6930100
[289] Szasz, A., Vincze, G., Szigeti, G. and Szasz, O. (2017) Internal Charge Redistribution and Currents in Cancerous Lesions. Journal of Advances in Biology, 10, 2061-2079.
[290] Lineweaver, C.H., Davies, P.C.W. and Vincent, M.D. (2014) Targeting Cancer’s Weaknesses (Not Its Strengths): Therapeutic Strategies Suggested by the Atavistic Model. Bioessays, 36, 827-835. https://doi.org/10.1002/bies.201400070

[291] Reid, B., McCaig, C.D., Zhao, M., et al. (2005) Wound Healing in Rat Cornea: The Role of Electric Currents. FASEB Journal, 19, 379-386. https://doi.org/10.1096/fj.04-2325com
[292] Balkwill, F. and Mantovani, A. (2001) Inflammation and Cancer: Back to Virchow? The Lancet, 357, 539-545. https://doi.org/10.1016/S0140-6736(00)04046-0
[293] Fiala, E.S., Sohn, O.S., Wang, C.X., et al. (2005) Induction of Preneoplastic Lung Lesions in Guinea Pigs by Cigarette Smoke Inhalation and their Exacerbation by High Dietary Levels of Vitamins C and E. Carcinogenesis, 26, 605-612. https://doi.org/10.1093/carcin/bgh341
[294] Murthy, N.S. and Mathew, A. (2000) Risk Factors for Pre-Cancerous Lesions of the Cervix. European Journal of Cancer Prevention, 9, 5-14. https://doi.org/10.1097/00008469-200002000-00002
[295] Molloy, R.M. and Sonnenberg, A. (1997) Relation between Gastric Cancer and Previous Peptic Ulcer Disease. Gut, 40, 247-252. https://doi.org/10.1136/gut.40.2.247
[296] Sundaram, G.M., Quah, S. and Sampath, P. (2018) Cancer: The Dark Side of Wound Healing. The FEBS Journal, 285, 4516-4534. https://doi.org/10.1111/febs.14586
[297] Schafer, M. and Werner, S. (2008) Cancer as an Overhealing Wound: An Old Hypothesis Revisited. Nature Reviews Molecular Cell Biology, 9, 628-638. https://doi.org/10.1038/nrm2455
[298] Dvorak, H.F. (2015) Tumors: Wounds That Do Not Heal—Redux. Cancer Immunology Research, 3, 1-11. https://doi.org/10.1158/2326-6066.CIR-14-0209
[299] Feng, Y., Santoriello, C., Mione, M., Hurlstone, A. and Martin, P. (2010) Live Imaging of Innate Immune Cell Sensing of Transformed Cells in Zebrafish Larvae: Parallels between Tumor Initiation and Wound Inflammation. PLOS Biology, 8, e1000562. https://doi.org/10.1371/journal.pbio.1000562
[300] Gionzalez, H., Hagerling, C. and Werb, Z. (2018) Roles of the Immune System in Cancer: From Tumor Initiation to Metastatic Progression. Genes and Development, 32, 1267-1284. https://doi.org/10.1101/gad.314617.118
[301] Jia, W., Li, H., Zhao, L., et al. (2008) Gut Microbiota: A Potential New Territory for Drug Targeting. Nature Reviews, 7, 123-129. https://doi.org/10.1038/nrd2505
[302] Hanausek, M., Walaszek, Z. and Slaga, T.J. (2003) Detoxifying Cancer Causing Agents to Prevent Cancer. Integrative Cancer Therapies, 2, 139-144. https://doi.org/10.1177/1534735403002002005
[303] Shankaran, V., Ikeda, H., Bruce, A.T., White, J.M., Swanson, P.E., Old, L.J. and Schreiber, R.D. (2001) IFNgamma and Lymphocytes Prevent Primary Tumour Development and Shape Tumour Immunogenicity. Nature, 410, 1107-1111. https://doi.org/10.1038/35074122
[304] Shankaran, V., Ikeda, H., Bruce, A.T., et al. (2018) Pillars Article: IFNgamma and Lymphocytes Prevent Primary Tumour Development and Shape Tumor Immunogenicity. The Journal of Immunology, 201, 827-831.
[305] Dunn, G.P., Old, L.J. and Schreiber, R.D. (2004) The Immunobiology of Cancer Immunosurveillance and Immunoediting. Immunity, 21, 137-148. https://doi.org/10.1016/j.immuni.2004.07.017
[306] Dunn, G.P., Koebel, C.M. and Schreiber, R.D. (2006) Interferons, Immunity and Cancer Immunoediting. Nature Reviews Immunology, 6, 836-848. https://doi.org/10.1038/nri1961
[307] Miller, J.S. (2001) The Biology of Natural Killer Cells in Cancer, Infection, and Pregnancy. Experimental Hematology, 29, 1157-1168. https://doi.org/10.1016/S0301-472X(01)00696-8
[308] Ghiringhelli, F., Menard, C., Martin, F. and Zitvogel, L. (2006) The Role of Regula- tory T Cells in the Control of Natural Killer Cells: Relevance during Tumor Progression. Immunological Reviews, 214, 229-238. https://doi.org/10.1111/j.1600-065X.2006.00445.x
[309] Honda, K. and Littman, D.R. (2016) The Microbiota in Adaptive Immune Homeostasis and Disease. Nature, 535, 75-84. https://doi.org/10.1038/nature18848
[310] Belkaid, Y. and Harrison, O.J. (2017) Homeostatic Immunity and the Microbiota. Immunity, 46, 562-567. https://doi.org/10.1016/j.immuni.2017.04.008
[311] Cholujova, D., Jakubikova, J. and Sedlak, J. (2009) Biobran-Augmented Maturation of Human Monocyte-Derived Dendritic Cells. Neoplasma, 56, 89-95. https://doi.org/10.4149/neo_2009_02_89
[312] Romero, D. (2019) From New Directions in Immuno-Oncology. Nature Reviews Clinical Oncology, 16, 660. https://doi.org/10.1038/s41571-019-0280-7
[313] Busch, W. (1868) Aus der Sitzung der medicinischen Section vom 13 November 1867. Berliner Klinische Wochenschrift, 5, 137.
[314] Burnet, F.M. (1970) The Concept of Immunological Surveillance. Progress in Experimental Tumor Research, 13, 1-27. https://doi.org/10.1159/000386035
[315] Akinleye, A. and Rasool, Z. (2019) Immune Checkpoint Inhibitors of PD-L1 as Cancer Therapeutics. Journal of Hematology & Oncology, 12, 92. https://doi.org/10.1186/s13045-019-0779-5
[316] Bakacs, T., Mehrishi, J.N. and Moss, R.W. (2012) Ipilimumab (Yervoy) and the TGN1412 Catastrophe. Immunobiology, 217, 583-589. https://doi.org/10.1016/j.imbio.2011.07.005
[317] Bakacs, T., Kristof, K., Mehrishi, J., et al. (2017) Autoimmune T-Cells Induced by Low Dose Immune Checkpoint Blockade Could Be a Powerful Therapeutic Tool in Cancer through Activation of

Eliminative Inflammation and Immunity. Internal Medicine Review, 3, 1-8. https://doi.org/10.18103/imr.v3i4.408

[318] Conklin, K.A. (2009) Dietary Antioxidants during Cancer Chemotherapy: Impact on Chemotherapeutic Effectiveness and Development of Side Effects. Nutrition and Cancer, 37, 1-18. https://doi.org/10.1207/S15327914NC3701_1

[319] Tait, P., Morris, B. and To, T. (2014) Core Palliative Medicines-Meeting the Needs of Non-Complex Community Patients. Australian Family Physician, 43, 29-32.

[320] International Association for Hospice and Palliative Care (IAHPC) (2013) World Health Organization (WHO) Essential Medicines in Palliative Care, Executive Summary. https://www.who.int/selection_medicines/committees/expert/19/applications/Pallia tiveCare_8_A_R.pdf

[321] WA Cancer and Palliative Care Network, Essential Palliative Care Medication Lists for Community Pharmacists and General Practitioners, Government of Western Australia, Department of Health, 2011. https://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Health%20Netw orks/WA%20Cancer%20and%20Palliative%20Care/Palliative%20care/Essential-Palliative-Care-Medication-Lists-for-Community-Pharmacists-and-General-Practit ioners.pdf

[322] Davies, A.M. Weinberg, U. and Palti, Y. (2013) Tumor Treating Fields: A New Frontier in Cancer Therapy. Annals of the New York Academy of Sciences, 1291, 86-95. https://doi.org/10.1111/nyas.12112

[323] Chu, X.Y., Huang, W., Meng, L.W., et al. (2019) Improving Antitumor Outcomes for Palliative Intratumoral Injection Therapy through Lecithin-Chitosan Nanoparticles Loading Paclitaxel-Cholesterol Complex. International Journal of Nanomedicine, 14, 689-705. https://doi.org/10.2147/IJN.S188667

[324] Liangruksa, M. (2011) Nanoscale Thermal Transport for Biological and Physical Applications. Dissertation, Virginia Polytechnic Institute and State University, Blacksburg.

[325] Govorov, A.O. and Richardson, H.H. (2007) Generating Heat with Metal Nanoparticles. NanoToday, 2, 30-38. https://doi.org/10.1016/S1748-0132(07)70017-8

[326] Gannon, C.J., Patra, C.R., Bhattacharya, R., et al. (2008) Intracellular Gold Nano- particles Enhance Non-Invasive Radiofrequency Thermal Destruction of Human Gastrointestinal Cancer Cells. Journal of Nanobiotechnology, 6, 2. https://doi.org/10.1186/1477-3155-6-2

[327] Szasz, A. (2015) Bioelectromagnetic Paradigm of Cancer Treatment Oncothermia. In: Rosch, P.J., Ed., Bioelectromagnetic and Subtle Energy Medicine, CRC Press, Taylor & Francis Group, Boca Raton, 323-336.

[328] Raoof, M., Cisneros, B.T., Corr, S.J., et al. (2013) Tumor Selective Hyperthermia Induced by Short-Wave Capacitively-Coupled RF Electric-Fields. PLOS ONE, 8, e68506. https://doi.org/10.1371/journal.pone.0068506

[329] Andocs, G., Rehman, M.U., Zhao, Q.L., Papp, E., Kondo, T. and Szasz, A. (2015) Nanoheating without Artificial Nanoparticles Part II. Experimental Support of the Nanoheating Concept of the Modulated Electro-Hyperthermia Method, Using U937 Cell Suspension Model. Biology and Medicine, 7, 1-9. https://doi.org/10.4172/0974-8369.1000247

[330] Kirson, E.D., Dbaly, V., Tovarys, F., et al. (2007) Alternating Electric Fields Arrest Cell Proliferation, in Animal Tumor Models and Human Brain Tumors. Proceedings of the National Academy of Sciences of the United States of America, 104, 10152-10157. https://doi.org/10.1073/pnas.0702916104

[331] Giladi, M., Munster, M., Schneiderman, R.S., et al. (2017) Tumor Treating Fields (Ttfields) Delay DNA Damage Repair Following Radiation Treatment of Glioma Cells. Radiation Oncology, 12, 206. https://doi.org/10.1186/s13014-017-0941-6

[332] Stupp, R., Tailibert, S., Kanner, A., et al. (2017) Effect of Tumor-Treating Fields plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients with Glioblastoma: A Randomized Clinical Trial. JAMA, 318, 2306-2316. https://doi.org/10.1001/jama.2017.18718

[333] Mun, E.J., Babiker, H.M., Weinber, U., et al. (2017) Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. Clinical Cancer Research, 24, 266-275. https://doi.org/10.1158/1078-0432.CCR-17-1117

[334] Szasz, O., Szigeti, G.P. and Szasz, A.M. (2017) Electrokinetics of Temperature for Development and Treatment of Effusions. Advances in Bioscience and Biotechnology, 8, 434-449. https://doi.org/10.4236/abb.2017.811032

[335] Pang, C.L.K., Zhang, X., et al. (2017) Local Modulated Electro-Hyperthermia in Combination with Malignant Ascites: A Phase II Randomized Trial. Molecular and Clinical Oncology, 6, 723-732. https://doi.org/10.3892/mco.2017.1221

[336] Vaupel, P.W. and Kelleher, D.K. (1996) Metabolic Status and Reaction to Heat of Normal and Tumor Tissue. In: Seegenschmiedt, M.H., Fessenden, P. and Vernon, C.C., Eds., Thermoradiotherapy and Thermochemotherapy: Biology, Physiology and Physics, Vol. 1, Springer Verlag, Berlin, 157-176. https://doi.org/10.1007/978-3-642-57858-8_8

[337] Ferenczy, G.L. and Szasz, A. (2020) Ch. 3. Technical Challenges and Proposals in Oncological Hyperthermia. In: Szasz, A., Ed., Challenges and Solutions of Oncological Hyperthermia, Cambridge Scholars, Newcastle upon Tyne, 72-90. https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[338] Szentgyorgyi, A. (1968) Bioelectronics: A Study on Cellular Regulations, Defence and Cancer. Acad. Press, New York.
[339] Szasz, O. (2013) Burden of Oncothermia—Why Is It Special? Conference Papers in Medicine, 2013, Article ID: 938689. http://www.hindawi.com/archive/2013/938689
[340] Fiorentini, G. and Szasz, A. (2006) Hyperthermia Today: Electric Energy, a New Opportunity in Cancer Treatment. Journal of Cancer Research and Therapeutics, 2, 41-46. https://doi.org/10.4103/0973-1482.25848
[341] Szasz, O. and Szasz, A. (2014) Oncothermia-Nano-Heating Paradigm. Journal of Cancer Science and Therapy, 6, 4. https://doi.org/10.4172/1948-5956.1000259
[342] Szasz, A. (2013) Chapter 4. Electromagnetic Effects in Nanoscale Range. In: Shimizu, T. and Kondo, T., Eds., Cellular Response to Physical Stress and Therapeutic Applications, Nova Science Publishers, Inc., Hauppauge.
[343] Vincze, G., Szigeti, G., Andocs, G. and Szasz, A. (2015) Nanoheating without Artificial Nanoparticles. Biology and Medicine, 7, 249.
[344] Prasad, B., Kim, S., Cho, W., et al. (2018) Effect of Tumor Properties on Energy Absorption, Temperature Mapping, and Thermal Dose in 13.56-MHz Radiofrequency Hyperthermia. Journal of Thermal Biology, 74, 281-289. https://www.ncbi.nlm.nih.gov/pubmed/29801639
[345] Lee, S.Y., Kim, J.H., et al. (2018) The Effect of Modulated Electro-Hyperthermia on Temperature and Blood Flow in Human Cervical Carcinoma. International Journal of Hyperthermia, 34, 953-960. https://doi.org/10.1080/02656736.2018.1423709
[346] Szasz, O. (2013) Essentials of Oncothermia. Conference Papers in Medicine, 2013, Article ID: 159570. https://doi.org/10.1155/2013/159570
[347] Wust, P., Ghadjar, P., Nadobny, J., et al. (2019) Physical Analysis of Temperature-Dependent Effects of Amplitude-Modulated Electromagnetic Hyperthermia. International Journal of Hypertension, 36, 1246-1254. https://doi.org/10.1080/02656736.2019.1692376
[348] Szasz, A., Szasz, N. and Szasz, O. (2010) Oncothermia-Principles and Practices. Springer Science, Heidelberg. http://www.springer.com/gp/book/9789048194971
[349] Szasz, O., Szasz, A.M., Minnaar, C. and Szasz, A. (2017) Heating Preciosity—Trends in Modern Oncological Hyperthermia. Open Journal of Biophysics, 7, 116-144. https://doi.org/10.4236/ojbiphy.2017.73010
[350] Andocs, G., Renner, H., Balogh, L., Fonyad, L., Jakab, C. and Szasz, A. (2009) Strong Synergy of Heat and Modulated Electromagnetic Field in Tumor Cell Killing. Strahlentherapie und Onkologie, 185, 120-126. https://doi.org/10.1007/s00066-009-1903-1
[351] Torok, Z., Crul, T., Maresca, B., et al. (2014) Plasma Membranes as Heat Stress Sensors: From Lipid-Controlled Molecular Switches to Therapeutic Applications. Biochimica et Biophysica Acta, 1838, 1594-1618. https://doi.org/10.1016/j.bbamem.2013.12.015
[352] Staunton, J.R., Wirtz, D., Tlsty, T.D., et al. (2013) A Physical Sciences Network Characterization of Non-Tumorigenic and Metastatic Cells. Scientific Reports, 3, Article No. 1449. https://doi.org/10.1038/srep01449
[353] Papp, E., Vancsik, T., Kiss, E. and Szasz, O. (2017) Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (mEHT). Open Journal of Biophysics, 7, 216-229. https://doi.org/10.4236/ojbiphy.2017.74016
[354] Szasz, O. (2013) Renewing Oncological Hyperthermia-Oncothermia. Open Journal of Biophysics, 3, 245-252. https://doi.org/10.4236/ojbiphy.2013.34030
[355] Szasz, O. (2019) Bioelectromagnetic Paradigm of Cancer Treatment-Modulated Electro-Hyperthermia (mEHT). OJBIPHY, 9, 98-109. https://doi.org/10.4236/ojbiphy.2019.92008
[356] Meggyeshazi, N. andocs, G., Balogh, L., et al. (2014) DNA Fragmentation and Caspase-Independent Programmed Cell Death by Modulated Electrohyperthermia. Strahlentherapie und Onkologie, 190, 815-822. http://www.ncbi.nlm.nih.gov/pubmed/24562547
[357] Yang, K.L., Huang, C.C., Chi, M.S., Chiang, H.C., Wang, Y.S. andocs, G., et al. (2016) In Vitro Comparison of Conventional Hyperthermia and Modulated Electro-Hyperthermia. Oncotarget, 7, 84082-84092. https://doi.org/10.18632/oncotarget.11444
[358] Andocs, G., Meggyeshazi, N., Balogh, L., et al. (2014) Upregulation of Heat Shock Proteins and the Promotion of Damage-Associated Molecular Pattern Signals in a Colorectal Cancer Model by Modulated Electrohyperthermia. Cell Stress and Chaperones, 20, 37-46. http://www.ncbi.nlm.nih.gov/pubmed/24973890

[359] Jeon, T.W., Yang, H., Lee, C.G., et al. (2016) Electro-Hyperthermia Up-Regulates Tumour Suppressor Septin 4 to Induce Apoptotic Cell Death in Hepatocellular Carcinoma. International Journal of Hypertension, 7, 1-9. https://doi.org/10.1080/02656736.2016.1186290
[360] Meggyeshazi, N. (2015) Studies on Modulated Electrohyperthermia Induced Tumor Cell Death in a Colorectal Carcinoma Model. Thesis, Pathological Sciences Doctoral School, Semmelweis University, Budapest. http://repo.lib.semmelweis.hu/handle/123456789/3956
[361] Andocs, G., Szasz, O. and Szasz, A. (2009) Oncothermia Treatment of Cancer: From the Laboratory to Clinic. Electromagnetic Biology and Medicine, 28, 148-165. https://doi.org/10.1080/15368370902724633
[362] Fiorentini, G., Sarti, D., Casadei, V., et al. (2019) Modulated Electro-Hyperthermia as Palliative Treatment for Pancreas Cancer: A Retrospective Observational Study on 106 Patients. Integrative Cancer Therapies, 18, 1-8. https://doi.org/10.1177/1534735419878505
[363] Szasz, A.M., Minnaar, C.A., Szentmartoni, G., et al. (2019) Review of the Clinical Evidences of Modulated Electro-Hyperthermia (Meht) Method: An Update for the Practicing Oncologist. Frontiers in Oncology, 9, Article No. 1012. https://doi.org/10.3389/fonc.2019.01012
[364] Minnaar, C.A., Kotzen, J.A., Ayeni, O.A., et al. (2019) The Effect of Modulated Electro-Hyperthermia on Local Disease Control in HIV-Positive and -Negative Cervical Cancer Women in South Africa: Early Results from a Phase III Randomized Controlled Trial. PLOS ONE, 14, e0217894. https://doi.org/10.1371/journal.pone.0217894
[365] Vincze, G., Szasz, O. and Szasz, A. (2015) Generalization of the Thermal Dose of Hyperthermia in Oncology. Open Journal of Biophysics, 5, 97-114. https://doi.org/10.4236/ojbiphy.2015.54009
[366] Vincze, G. and Szasz, A. (2018) Similarities of Modulation by Temperature and by Electric Field. OJBIPHY, 8, 95-103. https://doi.org/10.4236/ojbiphy.2018.83008
[367] Szasz, A., Vincze, G., Szasz, O. and Szasz, N. (2003) An Energy Analysis of Extracellular Hyperthermia. Magneto- and Electro-Biology, 22, 103-115. https://doi.org/10.1081/JBC-120024620
[368] Hegyi, G., Szasz, O. and Szasz, A. (2013) Oncothermia: A New Paradigm and Promising Method in Cancer Therapies. Acupuncture & Electro-Therapeutics Re- search: The International Journal, 38, 161-197. https://doi.org/10.3727/036012913X13831832269243
[369] Hegyi, G., Szigeti, G.P. and Szasz, A. (2013) Hyperthermia versus Oncothermia: Cellular Effects in Complementary Cancer Therapy. Evidence-Based Complementary and Alternative Medicine, 2013, Article ID: 672873. https://doi.org/10.1155/2013/672873
[370] Lee, S.Y., Szigeti, G.P. and Szasz, A.M. (2018) Oncological Hyperthermia: The Correct Dosing in Clinical Applications. International Journal of Oncology, 54, 627-643. https://doi.org/10.3892/ijo.2018.4645
[371] Hager, D., Dziambor, H., Hoehmann, D., et al. (2002) Survival and Quality of Life of Patients with Advanced Pancreatic Cancer. Annual Meeting of the American Society of Clinical Oncology, Orlando, 18-21 May 2002, 2359.
[372] Ou, J., Zhu, X., Chen, P., et al. (2020) 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. Journal of Advanced Research, 24, 175-182. https://www.ncbi.nlm.nih.gov/pubmed/32368355
[373] Prasad, B., Kim, S., Cho, W., et al. (2019) Quantitative Estimation of the Equivalent Radiation Dose Escalation Using Radiofrequency Hyperthermia in Mouse Xeno- graft Models of Human Lung Cancer. Scientific Reports, 9, Article No. 3942. https://doi.org/10.1038/s41598-019-40595-6
[374] Vancsik, T., Forika, G., Balogh, A., et al. (2019) Modulated Electro-Hyperthermia Induced P53 Driven Apoptosis and Cell Cycle Arrest Additively Support Doxorubicin Chemotherapy of Colorectal Cancer in Vitro. Cancer Medicine, 8, 4292-4303. https://doi.org/10.1002/cam4.2330
[375] Tsang, Y.W., Chi, K.H., et al. (2019) Modulated Electro-Hyperthermia-Enhanced Liposomal Drug Uptake by Cancer Cells. International Journal of Nanomedicine, 14, 1269-1579. https://doi.org/10.2147/IJN.S188791
[376] Roussakow, S. (2013) The History of Hyperthermia Rise and Decline. Conference Papers in Medicine, 2013, Article ID: 201671. http://www.hindawi.com/journals/cpis/2013/428027
[377] Szasz, A., Szasz, N. and Szasz, O. (2013) Local Hyperthermia in Oncology—to Choose or Not to Choose? In: Huilgol, N., Ed., Hyperthermia, InTech, London, 1-82. https://doi.org/10.5772/52208
[378] Vernon, C.C., Hand, J.W., Field, S.B., et al. (1996) Radiotherapy with or without Hyperthermia in the Treatment of Superficial Localized Breast Cancer: Results from Five Randomized Controlled Trials. International Journal of Radiation Oncology, Biology, Physics, 35, 731-744. https://doi.org/10.1016/0360-3016(96)00154-X
[379] Sherar, M., Liu, F.F., Pintilie, M., et al. (1997) Relationship between Thermal Dose and Outcome in Thermoradiotherapy Treatments for Superficial Recurrences of Breast Cancer: Data from a Phase III Trial. International Journal of Radiation Oncology, Biology, Physics, 39, 371-380. https://doi.org/10.1016/S0360-3016(97)00333-7

[380] Zolciak-Siwinska, A., Piotrokowicz, N., Jonska-Gmyre, J., et al. (2013) HDR Brachytherapy Combined with Interstitial Hyperthermia in Locally Advanced Cervical Cancer Patients Initially Treated with Concomitant Radiochemotherapy—A Phase III Study. Radiotherapy and Oncology, 109, 194-199. https://doi.org/10.1016/j.radonc.2013.04.011

[381] Kay, C.S., Choi, I.B., Jang, J.Y., Choi, B.O., Kim, I.A., Shinn, K.S., et al. (1996) Thermoradiotherapy in the Treatment of Locally Advanced Nonsmall Cell Lung Cancer. The Journal of the Korean Society for Therapeutic Radiology and Oncology, 14, 115-122. https://doi.org/10.1016/0169-5002(96)85955-1

[382] Jones, E.L., Oleson, J.R., Prosnith, L.R., et al. (2007) Randomized Trial of Hyperthermia and Radiation for Superficial Tumours. Journal of Clinical Oncology, 23, 3079-3085. https://doi.org/10.1200/JCO.2005.05.520

[383] Mitsumori, M., Zhi-Fan, Z., Oliynychenko, P., et al. (2007) Regional Hyperthermia Combined with Radiotherapy for Locally Advanced Non-Small Cell Lung Cancers: A Multi-Institutional Prospective Randomized Trial of the International Atomic Energy Agency. International Journal of Clinical Oncology, 12, 192-198. https://doi.org/10.1007/s10147-006-0647-5

[384] Barker, A.T., Jaffe, L.F. and Vanable, J.W. (1982) The Glabrous Epidermis of Cavies Contains a Powerful Battery. American Journal of Physiology, 242, R358-R366. https://doi.org/10.1152/ajpregu.1982.242.3.R358

[385] Rosch, P.J. and Markov, M.S. (2004) Bioelectromagnetic Medicine. Marcell Decker Inc., New York. https://doi.org/10.3109/9780203021651

[386] Samuelsson, L., Jonsson, L. and Stahl, E. (1983) Percutaneous Treatment of Pulmonary Tumors by Electrolysis. Radiologie, 23, 284-287. https://doi.org/10.1016/0011-2275(83)90154-6

[387] Song, B., Zhao, M., Forrester, J., et al. (2004) Nerve Regeneration and Wound Healing Are Stimulated and Directed by an Endogenous Electrical Field in Vivo. Journal of Cell Science, 117, 4681-4690. https://doi.org/10.1242/jcs.01341

[388] Carbon, M., Wübbeler, G., Mackert, B.M., et al. (2004) Non-Invasive Magnetic Detection of Human Injury Currents. Clinical Neurophysiology, 115, 1027-1032. https://doi.org/10.1016/j.clinph.2003.12.035

[389] Reid, B., Nuccitelli, R. and Zhao, M. (2007) Non-Invasive Measurement of Bioelectric Currents with a Vibrating Probe. Nature Protocols, 2, 661-669. https://doi.org/10.1038/nprot.2007.91

[390] Mackert, B.M., Mackert, J., Wübbeler, G., et al. (1999) Magnetometry of Injury Currents from Human Nerve and Muscle Specimens Using Superconducting Quantum Interferences Devices. Neuroscience Letters, 262, 163-166. https://doi.org/10.1016/S0304-3940(99)00067-1

[391] Zhao, M., Forrester, J.V. and McCaig, C.D. (1999) A Small, Physiological Electric Field Orients Cell Division. Proceedings of the National Academy of Sciences of the United States of America, 96, 4942-4946. https://doi.org/10.1073/pnas.96.9.4942

[392] Song, B., Zhao, M., Forrester, J.V., et al. (2002) Electrical Cues Regulate the Orientation and Frequency of Cell Division and the Rate of Wound Healing in Vivo. PNAS, 99, 13577-13582. https://doi.org/10.1073/pnas.202235299

[393] Zhao, M. (2009) Electrical Fields in Wound Healing—An Overriding Signal That Directs Cell Migration. Seminars in Cell & Developmental Biology, 20, 674-682. https://doi.org/10.1016/j.semcdb.2008.12.009

[394] Huttenlocher, A. (2007) Wound Healing with Electric Potential. NEJM, 356, 304-305. https://doi.org/10.1056/NEJMcibr066496

[395] Becker, R.O. and Selden, G. (1985) The Body Electric. Morrow, New York.

[396] Becker, R.O. (1990) Cross Currents. Jeremy P Tarcher Inc., Los Angeles.

[397] McCaig, C.D., Rajnicek, A.M., Song, B., et al. (2005) Controlling Cell Behaviour Electrically: Current Views and Future Potential. Physiological Reviews, 85, 943-978. https://doi.org/10.1152/physrev.00020.2004

[398] Rosenberg, S.M. and Queitsch, C. (2014) Combating Evolution to Fight Disease. Science, 343, 1088-1089. https://doi.org/10.1126/science.1247472

[399] Galluzzi, L., Zitvogel, L. and Kroemer, G. (2016) Immunological Mechanisms underneath the Efficacy of Cancer Therapy. Cancer Immunology Research, 4, 895-902. https://doi.org/10.1158/2326-6066.CIR-16-0197

[400] Waldhauer, I. and Steinle, A. (2008) NK Cells and Cancer Immunosurveillance. Oncogene, 27, 5932-5943. https://doi.org/10.1038/onc.2008.267

[401] Zamai, L., Ponti, C., Mirandola, P., et al. (2007) NK Cells and Cancer. The Journal of Immunology, 178, 4011-4016. https://doi.org/10.4049/jimmunol.178.7.4011

[402] Hu, W., Wang, G., Huang, D., et al. (2019) Cancer Immunotherapy Based on Natural Cell Killer Cells: Current Progress and New Opportunities. Frontiers in Immunology, 10, Article No. 1205. https://doi.org/10.3389/fimmu.2019.01205

[403] Bassani, B., Baci, D. and Gallazzi, M. (2019) Natural Killer Cells as Key Players of Tumor Progression and Angiogenesis: Old and Novel Tools to Divert Their Pro-Tumor Activities into Potent Anti-Tumor Effects. Cancers, 11, 461. https://doi.org/10.3390/cancers11040461
[404] Betten, A., Dahlgren, C., Mellqvist, U.H., et al. (2004) Oxygen Radical-Induced Natural Killer Cell Dysfunction: Role of Myeloperosicase and Regulation by Serotonin. Journal of Leukocyte Biology, 75, 1111-1115. https://doi.org/10.1189/jlb.1103595
[405] Sag, D., Ayyildiz, Z.O., Gunalp, S., et al. (2019) The Role of TRAIL/Drs in the Modulation of Immune Cells and Responses. Cancers, 11, 1469. https://doi.org/10.3390/cancers11101469
[406] Wajant, H. (2019) Molecular Mode of Action of TRAIL Receptor Agonists Common Principles and Their Translational Exploitation. Cancers, 11, 954. https://doi.org/10.3390/cancers11070954
[407] Mifsud, E.J., Tan, A.C.L. and Jacks, D.C. (2014) TLR Agonists as Modulators of the Innate Immune Response and Their Potential as Agents against Infectious Disease. Frontiers in Immunology, 5, Article No. 79. https://doi.org/10.3389/fimmu.2014.00079
[408] Meggyeshazi, N. andocs, G., et al. (2013) Early Changes in mRNA and Protein Expression Related to Cancer Treatment by Modulated Electro-Hyperthermia. Conference Papers in Medicine, 2013, Article ID: 249563. http://www.hindawi.com/archive/2013/249563
[409] Masuda, Y., Nawa, D. and Nakayama, Y. (2015) Soluble b-Glucan from Grifola frondosa Induces Tumor Regression in Synergy with TLR9 Agonist via Dendritic Cell-Mediated Immunity. Journal of Leukocyte Biology, 98, 1015-1025. https://doi.org/10.1189/jlb.1A0814-415RR
[410] Showalter, A., Limaye, A. and Oyer, J.L. (2017) Cytokines in Immunogenic Cell Death: Applications for Cancer Immonotherapy. Cytokine, 97, 123-132. https://doi.org/10.1016/j.cyto.2017.05.024
[411] Krysko, O., Aaes, T.L. and Bachert, C. (2013) Many Faces of DAMPs in Cancer Therapy. Cell Death and Disease, 4, e631. https://doi.org/10.1038/cddis.2013.156
[412] Hernandez, C., Huebener, P. and Schwabe, R.F. (2016) Damage Associated Mole- cular Patterns in Cancer: A Double-Edged Sword. Oncogene, 35, 5931-5941. https://doi.org/10.1038/onc.2016.104
[413] Repasky, E.A. and Evans, S.S. (2013) Temperature Matters! And Why It Should Matter to Tumor Immunologists. Cancer Immunology Research, 1, 210-216. https://doi.org/10.1158/2326-6066.CIR-13-0118
[414] Dieing, A., Ashlers, O. and Hildebrandt, B. (2007) The Effect of Induced Hyperthermia on the Immune System. Progress in Brain Research, 162, 137-152. https://doi.org/10.1016/S0079-6123(06)62008-6
[415] Sulyok, I., Fleishmann, E. and Stift, A. (2012) Effect of Preoperative Fever-Range Whole-Body Hyperthermia on Immunological Markers in Patients Undergoing Colorectal Cancer Surgery. British Journal of Anaesthesia, 109, 754-761. https://doi.org/10.1093/bja/aes248
[416] Shen, R.N., Lu, L., Young, P., Shidnia, H., Hornback, N.B. and Broxmeyer, H.E. (1994) Influence of Elevated Temperature on Natural Killer Cell Activity, Lymphokine-Activated Killer Cell Activity and Lecitin-Dependent Cytotoxicity of Human Umbilical Cord Blood and Adult Blood Cell. International Journal of Radiation Oncology, Biology, Physics, 29, 821-826. https://doi.org/10.1016/0360-3016(94)90571-1
[417] Hietanen, T., Kapanen, M. and Kellokumpu-Lehtinen, P.L. (2016) Restoring Natural Killer Cell Cytotoxicity after Hyperthermia Alone or Combined with Radiotherapy. Anticancer Research, 36, 555-564.
[418] Beachy. S.H. and Repasky, E.A. (2011) Toward Establishment of Temperature Thresholds for Immunological Impact of Heat Exposure in Humans. International Journal of Hyperthermia, 27, 344-352. https://doi.org/10.3109/02656736.2011.562873
[419] Staunton, J.R., et al. (2008) The Physical Sciences-Oncology Centers Network, a Physical Sciences Network Characterization of Non-Tumorigenic and Metastatic Cells. Scientific Reports, 3, Article No. 1449.
[420] Szasz, A. (2019) Thermal and Nonthermal Effects of Radiofrequency on Living State and Applications as an Adjuvant with Radiation Therapy. Journal of Radiation and Cancer Research, 10, 1-17. https://doi.org/10.4103/jrcr.jrcr_25_18
[421] Vincze, G. and Szasz, A. (2015) Effect of Cellular Membrane Resistivity Inhomogeneity on the Thermal Noise-Limit. Journal of Advances in Physics, 11, 3170-3183. https://doi.org/10.24297/jap.v11i3.6859
[422] Ye, L., Zhang, T. and Kang, Z. (2019) Tumor-Infiltrating Immune Cells Act as a Marker for Prognosis in Colorectal Cancer. Frontiers in Immunology, 10, Article No. 2368. https://doi.org/10.3389/fimmu.2019.02368
[423] Mole, R.H. (1953) Whole Body Irradiation-Radiology or Medicine? British Journal of Radiology, 26, 234-241. https://doi.org/10.1259/0007-1285-26-305-234
[424] Cavanagh, W. (2009) The Abscopal Effect and the Prospect of Using Cancer against Itself, Prostate Cancer Research Institute. PCRI Insights, Vol. 12.1.
[425] Wersäll, P.J., Blomgren, H., Pisa, P., Lax, I., Kälkner, K.M. and Svedman, C. (2006) Regression of Non-Irradiated Metastases after Extracranial Stereotactic Radiotherapy in Metastatic Renal Cell Carcinoma. Acta Oncologica, 45, 493-497. https://doi.org/10.1080/02841860600604611

[426] Trott, K.R. (2001) Non-Targeted Radiation Effects in Radiotherapy-Roles of Radiation-Induced Genomic Instability and of the Bystander Effect in Cancer Cure by Radiotherapy. Acta Oncologica, 40, 976-980. https://doi.org/10.1080/02841860152708260
[427] Hartford, A., Gohongi, T., Fukumura, D. and Jain, R. (2000) Irradiation of a Primary Tumor, Unlike Surgical Removal, Enhances Angiogenesis Suppression at a Distal Site: Potential Role of Host-Tumor Interaction. Cancer Research, 60, 2128-2131.
[428] Uchida, A., Mizutani, Y., Nagamuta, M. and Ikenaga, M. (1989) Elevation of Sensitivity of Tumor Cells and Lytic Function of NK Cells. Immunopharmacology and Immunotoxicology, 11, 507-519. https://doi.org/10.3109/08923978909005381
[429] Tubin, S. and Raunik, W. (2017) Hunting for Abscopal and Bystander Effects: Clinical Exploitation of Non-Targeted Effects Induced by Partial High-Single-Dose Irradiation of the Hypoxic Tumour Segment in Oligometastatic Patients. Acta Oncologica, 56, 1333-1339. https://doi.org/10.1080/0284186X.2017.1346385
[430] Pouget, J.P., Georgakilas, A.G. and Ravanat, J.L. (2018) Targeted and Off-Target (Bystander and Abscopal) Effects of Radiation Therapy: Redox Mechanism and Risk/Benefit Analysis. Antioxidant & Redox Signaling, 29, 1447-1487. https://doi.org/10.1089/ars.2017.7267
[431] Wang, R., Zhou, T., Liu, W. and Zuo, L. (2018) Molecular Mechanism of Bystander Effects and Related Abscopal/Cohort Effects in Cancer Therapy. Oncotarget, 9, 18637-18647. https://doi.org/10.18632/oncotarget.24746
[432] Demaria, S., Ng, B., Devitt, M.L., Babb, J.S., Kawashima, N., Liebes, L. and Formenti, S.C. (2004) Ionizing Radiation Inhibition of Distant Untreated Tumors (Abscopal Effect) Is Immune Mediated. International Journal of Radiation Oncology, Biology, Physics, 58, 862-870. https://doi.org/10.1016/j.ijrobp.2003.09.012
[433] Kaminski, J.M., Shinohara, E., Summers, J.B., Niermann, K.J., Morimoto, A. and Brousal, J. (2005) The Controversial Abscopal Effect. Cancer Treatment Reviews, 31, 159-172. https://doi.org/10.1016/j.ctrv.2005.03.004
[434] Porter, D.L., Levine, B.L., Kalos, M., Bagg, A. and June, C.H. (2011) Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. The New England Journal of Medicine, 365, 725-733. https://doi.org/10.1056/NEJMoa1103849
[435] Nobler, M. (1969) The Abscopal Effect in Malignant Lymphoma and Its Relationship Tolymphocyte Circulation. Radiology, 93, 410-412. https://doi.org/10.1148/93.2.410
[436] Antoniades, J., Brady, L. and Lightfoot, D. (1977) Lymphangiographic Demonstration of the Abscopal Effect in Patients with Malignant Lymphomas. International Journal of Radiation Oncology, Biology, Physics, 2, 141-147. https://doi.org/10.1016/0360-3016(77)90020-7
[437] Formenti, S.C. and Demaria, S. (2009) Systemic Effects of Local Therapy. The Lancet Oncology, 10, 718-726. https://doi.org/10.1016/S1470-2045(09)70082-8
[438] Rees, G.J. (1981) Abscopal Regression in Lymphoma: A Mechanism in Common with Total Body Irradiation? Clinical Radiology, 32, 475-480. https://doi.org/10.1016/S0009-9260(81)80310-8
[439] Ehlers, G. and Fridman, M. (1973) Abscopal Effect of Radiation in Papillary Adenocarcinoma. The British Journal of Radiology, 46, 220-222. https://doi.org/10.1259/0007-1285-46-543-220
[440] Kingsley, D. (1975) An Interesting Case of Possible Abscopal Effect in Malignant Melanoma. The British Journal of Radiology, 48, 863-866. https://doi.org/10.1259/0007-1285-48-574-863
[441] Rees, G. and Ross, C. (1983) Abscopal Regression Following Radiotherapy for Adenocarcinoma. The British Journal of Radiology, 56, 63-66. https://doi.org/10.1259/0007-1285-56-661-63
[442] Rees, G.J.G., Ross, C.M.D. and Path, F.R.C. (1983) Abscopal Regression Following Radiotherapy for Adenocarcinoma. British Journal of Radiology, 56, 63-66. https://doi.org/10.1259/0007-1285-56-661-63
[443] Lakshmanagowda, P.B., Viswanath, L., Thimmaiah, N., Dasappa, L., Supe, S.S. and Kallur, P. (2009) Abscopal Effect in a Patient with Chronic Lymphocytic Leukemia during Radiation Therapy: A Case Report. Cases Journal, 2, 204. https://www.casesjournal.com/content/2/1/204
[444] Sham, R. (1995) The Abscopal Effect and Chronic Lymphocytic Leukemia. The American Journal of Medicine, 98, 307-308. https://doi.org/10.1016/S0002-9343(99)80380-5
[445] Smith, J.A. and Herr, H.W. (1979) Spontaneous Regression of Pulmonary Metastases from Transitional Cell Carcinoma. Cancer, 46, 1499-1502. https://doi.org/10.1002/1097-0142(19800915)46:6<1499::AID-CNCR2820460634>3. 0.CO;2-G
[446] Van der Meeren, A., Monti, P., Vandamme, M., Squiban, C., Wysocki, J. and Griffiths, N. (2005) Abdominal Radiation Exposure Elicits Inflammatory Responses and Abscopal Effects in the Lungs of Mice. Radiation Research, 163, 144-152. https://doi.org/10.1667/RR3293
[447] Ohba, K., Omagari, K., Nakamura, T., Ikuno, N., Saeki, S., Matsuo, I., Kinoshita, H., Masuda, J., Hazama, H., Sakamoto, I. and Kohno, S. (1998) Abscopal Regression of Hepatocellular Carcinoma after Radiotherapy for Bone Metastasis. Gut, 43, 575-577. https://doi.org/10.1136/gut.43.4.575

[448] Nakanishi, M., Chuma, M., Hige, S. and Asaka, M. (2008) Abscopal Effect on Hepatocellular Carcinoma. The American Journal of Gastroenterology, 103, 1320-1321. https://doi.org/10.1111/j.1572-0241.2007.01782_13.x
[449] Menon, H., Chen, D. and Ramapriyan, R. (2019) Influence of Low-Dose Radiation on Abscopal Responses in Patients Receiving High-Dose Radiation and Immuno- therapy. Journal for ImmunoTherapy of Cancer, 7, 237. https://doi.org/10.1186/s40425-019-0718-6
[450] Zahidunnabi, M., et al. (2009) Fractionated But Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect When Combined with Anti-CTLA-4 Antibody. Clinical Cancer Research, 15, 5379-5388. https://doi.org/10.1158/1078-0432.CCR-09-0265
[451] Liu, Y., Dong, Y. and Kong, L. (2018) Abscopal Effect of Radiotherapy Combined with Immune Checkpoint Inhibitors. Journal of Hematology & Oncology, 11, 104. https://doi.org/10.1186/s13045-018-0647-8
[452] Dagoglu, N., Karaman, S., Caglar, H.B., et al. (2019) Abscopal Effect of Radiotherapy in the Immunotherapy Era: Systematic Review of Reported Cases. Cureus, 11, e4103. https://doi.org/10.7759/cureus.4103
[453] Lauber, K. and Dunn, L. (2019) Immunotherapy Mythbusters in Head and Neck Cancer: The Abscopal Effect and Pseudoprogression. American Society of Clinical Oncology Educational Book, 39, 352-363. https://doi.org/10.1200/EDBK_238339
[454] Liu, J. and Mackley, H.B. (2019) Combining Immunotherapy with Radiation Therapy to Induce the Abscopal Response: What Clinical and Treatment Variables Matter? Applied Radiation Oncology, 8, 13-19.
[455] Yilmaz, M.T., Elmali, A. and Yazici, G. (2019) Abscopal Effect: From Myth to Reality from Radiation Oncologists' Perspective. Cureus, 11, e3860. https://doi.org/10.7759/cureus.3860
[456] Seidi, K., Zarghami, N. and Jahanban-Esfahlan, R. (2013) Proposed Approach for Revealing Unknown Mediators of Abscopal. Journal of Medical Hypotheses and Ideas, 7, 43-49. https://doi.org/10.1016/j.jmhi.2013.03.001
[457] Keisari, Y. (2013) Tumor Ablation, Effects on Systemic and Local Anti-Tumor Immunity and on Other Tumor-Microenvironment. Springer, Berlin. https://doi.org/10.1007/978-94-007-4694-7
[458] Wang, H., Zhang, L. and Shi, Y. (2013) Abscopal Antitumor Immune Effects of Magnet-Mediated Hyperthermia at a High Therapeutic Temperature on Walker-256 Carcinosarcomas in Rats. Oncology Letters, 7, 764-770. https://doi.org/10.3892/ol.2014.1803
[459] Persson, B.R.R., Koch, C., Graftsröm, G., et al. (2004) Abscopal Regression of Subcutaneously Implanted N29 Rat Glioma after Treatment of the Contra-Lateral Tumours with Pulsed Electric Fields (PEF) or Radiation Therapy (RT) and Their Combinations (PEF+RT). Cancer Therapy, 2, 533-548. https://doi.org/10.1177/153303460300200512
[460] Falk, R.E., Moffa, F.L. and Lawler, M. (1985) Combination Therapy for Resectable and Unresectable Adenocarcinoma of the Pancreas. Cancer, 57, 685-688. https://doi.org/10.1002/1097-0142(19860201)57:3<685::AID-CNCR2820570348>3.0.CO;2-X
[461] Oei, A.L., Korangath, P. and Mulka, K. (2019) Enhancing the Abscopal Effect of Radiation and Immune Checkpoint Inhibitor Therapies with Magnetic Nanoparticle Hyperthermia in a Model of Metastatic Breast Cancer. International Journal of Hyperthermia, 36, 47-63. https://doi.org/10.1080/02656736.2019.1685686
[462] Dank, M., Meggyeshazi, N., Szigeti, G. and Andocs, G. (2016) Immune Effects by Selective Heating of Membrane Rafts of Cancer-Cells. Journal of Clinical Oncology, 34, e14571. https://meetinglibrary.asco.org/record/124231/abstract
[463] Ngwa, W., Irabor, O.C. and Schoenfield, J.D. (2018) Using Immunotherapy to Boost the Abscopal. Nature Reviews Cancer, 18, 313-322. https://doi.org/10.1038/nrc.2018.6
[464] Honkoop, A.H., Luykx-de, Bakker, S.A., Hoekman, K., Meyer, S., Meyer, O.W., van Groeningen, C.J., van Diest, P.J., Boven, E., van der Wall, E., Giaccone, G., Wagstaff, J. and Pinedo, H.M. (1999) Prolonged Neoadjuvant Chemotherapy with GM-CSF in Locally Advanced Breast Cancer. Oncologist, 4, 106-111. https://doi.org/10.1634/theoncologist.4-2-106
[465] Spitler, L.E., Weber, R.W., Allen, R.E., Meyer, J., Cruickshank, S., Garbe, E., Lin, H.Y. and Soong, S.J. (2009) Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF, Ssargramostim) Administered for 3 Years as Adjuvant Therapy of Stages II(T4), III, and IV Melanoma. Journal of Immunotherapy, 32, 632-637. https://doi.org/10.1097/CJI.0b013e3181a7d60d
[466] Leary, R., Gardner, R.B. and Mockbee, C. (2019) Boosting Abscopal Response to Radiotherapy with Sargramostim: A Review of Data and Ongoing Studies. Cureus, 11, e4276. https://doi.org/10.7759/cureus.4276
[467] Fiorentini, G., Yoon, S.M., Yan, O. andocs, G., Baronzio, G.F., Laurent, S., Balogh, L. and Szasz, A. (2013) Abscopal Effect: New Perspectives in Oncothermia. Oncothermia Journal, 7, 279-281.

https://oncotherm.com/sites/oncotherm/files/2017-07/Abscopal_effect_new_perspe ctives_in_Oncothermia_T.pdf
[468] Andocs, G., Meggyeshazi, N., Okamoto, Y., Balogh, L. and Szasz, O. (2013) Bystander Effect of Oncothermia. Conference Papers in Medicine, 2013, Article ID: 953482. https://doi.org/10.1155/2013/953482
[469] Derer, A., Deloch, L. and Rubner, Y. (2015)-Radio-Immunotherapy-Induced Immunogenic Cancer Cells as Basis for Induction of Systemic Anti-Tumor Immune Responses-pre-Clinical Evidence and Ongoing Clinical Applications. Frontiers in Immunology, 6, Article No. 505. https://doi.org/10.3389/fimmu.2015.00505
[470] Vancsik, T., Kovago, C., Kiss, E., et al. (2018) Modulated Electro-Hyperthermia Induced Loco-Regional and Systemic Tumor Destruction in Colorectal Cancer Allografts. Journal of Cancer, 9, 41-53. https://doi.org/10.7150/jca.21520
[471] Qin, W., Akutsu, Y. andocs, G., et al. (2014) Modulated Electro-Hyperthermia Enhances Dendritic Cell Therapy through an Abscopal Effect in Mice. Oncology Re- ports, 32, 2373-2379. https://doi.org/10.3892/or.2014.3500
[472] Tsang, Y.W., Huang, C.C., Yang, K.L., et al. (2015) Improving Immunological Tu- mor Microenvironment Using Electro-Hyperthermia Followed by Dendritic Cell Immunotherapy. BMC Cancer, 15, Article No. 708. https://doi.org/10.1186/s12885-015-1690-2
[473] Andocs, G., Szasz, A., Szasz, O. and Iluri, N. (2016) Tumor Vaccination Patent. EP2780024B1. US20150217099A1. https://patents.google.com/patent/EP2780024B1/en
[474] Iyikesici, M.S., Slocum, A.K., Slocum, A., et al. (2017) Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer. Cureus, 9, e1445. https://doi.org/10.7759/cureus.1445
[475] Schirrmacher, V. (2015) Oncolytic Newcastle Disease Virus as a Prospective Anti-Cancer Therapy. A Biologic Agent with Potential to Break Therapy Resistance. Expert Opinion on Biological Therapy, 15, 1757-1771. https://doi.org/10.1517/14712598.2015.1088000
[476] Schirrmacher, V., Lorenzen, D., Van Gool, S.W., et al. (2017) A New Strategy of Cancer Immunotherapy Combining Hyperthermia/Oncolytic Virus Pretreatment with Specific Autologous Anti-Tumor Vaccination—A Review. Austin Oncology Case Reports, 2, 1006. https://doi.org/10.26420/austinoncolcaserep.1006.2017
[477] Schirrmacher, V., Stücker, W., Lulei, M., et al. (2015) Long-Term Survival of a Breast Cancer Patient with Extensive Liver Metastases upon Immune and Virotherapy: A Case Report. Immunotherapy, 7, 855-860. https://doi.org/10.2217/imt.15.48
[478] Schirrmacher, V., Bihari, A.S., Stücker, W., et al. (2014) Long-Term Remission of Prostate Cancer with Extensive Bone Metastases upon Immuno- and Virotherapy: A Case Report. Oncology Letters, 8, 2403-2406. https://doi.org/10.3892/ol.2014.2588
[479] Van Gool, S.W., Makalowski, J., Feyen, O., Prix, L., Schirrmacher, V. and Stuecker, W. (2018) The Induction of Immunogenic Cell Death (ICD) during Maintenance Chemotherapy and Subsequent Multimodal Immunotherapy for Glioblastoma (GBM). Austin Oncology Case Reports, 3, 1010.
[480] Ben-Jacob, E. (2013) Engineering Trojan-Horse Bacteria to Fight Cancer. Inside Blood, 122, 705-706. https://doi.org/10.1182/blood-2013-06-508481
[481] Kleef, R., Kekic, S. and Ludwig, N. (2012) Successful Treatment of Advanced Ovarian Cancer with Thermochemotherapy and Adjuvant Immune Therapy. Case Reports in Oncology, 5, 212-215. https://doi.org/10.1159/000338617
[482] Minnaar, C.A., Szigeti, G.P., et al. (2018) Modulated Electro-Hyperthermia as a Monotherapy: A Potential for Further Research? 36th ICHS Conference, Budapest, 28-29 September 2018.
[483] Roussakow, S. (2017) Clinical and Economic Evaluation of Modulated Electrohyperthermia Concurrent to Dose-Dense Temozolomide 21/28 Days Regimen in the Treatment of Recurrent Glioblastoma: A Retrospective Analysis of a Two-Centre German Cohort Trial with Systematic Comparison and Effect-to-Treatment Analysis. BMJ Open, 7, e017387. http://bmjopen.bmj.com/content/bmjopen/7/11/e017387.full.pdf
[484] Hager, E.D., Sahinbas, H., Groenemeyer, D.H., et al. (2008) Prospective Phase II Trial for Recurrent High-Grade Malignant Gliomas with Capacitive Coupled Low Radio- frequency (LRF) Deep Hyperthermia. Journal of Clinical Oncology, (Post-Meeting Edition), 26, 2047. https://doi.org/10.1200/jco.2008.26.15_suppl.2047
[485] Sahinbas, H., Groenemeyer, D.H.W., Boecher, E. and Szasz, A. (2007) Retrospective Clinical Study of Adjuvant Electro-Hyperthermia Treatment for Advanced Brain-Gliomas. Deutsche Zeitschrift fuer Onkologie, 39, 154-160. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2007-9860 20
[486] Fiorentini, G., Sarti, D., Milandri, C., et al. (2018) Modulated Electrohyperthermia in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: Retrospective Multicenter

Controlled Study. Integrative Cancer Therapies, 18, 1534735418812691. https://www.ncbi.nlm.nih.gov/pubmed/30580645
[487] Szasz, A. (2014) Current Status of Oncothermia Therapy for Lung Cancer. The Korean Journal of Thoracic and Cardiovascular Surgery, 47, 77-93. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4000888
[488] Lee, D.J., Haam, S.J., Kim, T.H., et al. (2013) Oncothermia with Chemotherapy in the Patients with Small Cell Lung Cancer. Conference Papers in Medicine, 2013, Article ID: 910363. http://www.hindawi.com/archive/2013/910363
[489] Lee, S.Y., Lee, N.R., Cho, D.H., et al. (2017) Treatment Outcome Analysis of Chemotherapy Combined with Modulated Electro-Hyperthermia Compared with Chemotherapy Alone for Recurrent Cervical Cancer, Following Irradiation. Oncology Letters, 14, 73-78. http://www.spandidos-publications.com/10.3892/ol.2017.6117
[490] Jeung, T.S., Ma, S.Y., Yu, J., et al. (2013) Cases that Respond to Oncothermia Monotherapy. Conference Papers in Medicine, 2013, Article ID: 392480. https://www.hindawi.com/journals/cpis/2013/392480 https://doi.org/10.1155/2013/392480
[491] Nixon, R. (1971) National Cancer Act. The Time of Declaration. https://www.cancer.gov/about-nci/overview/history/national-cancer-act-1971
[492] Yeung, K.S., Gubili, J. and Mao, J.J. (2018) Herb-Drug Interactions in Cancer Care. Oncology (Williston Park), 32, 516-520.
[493] McEwen, B.S. (2006) Protective and Damaging Effects of Stress Mediators: Central Role of the Brain. Dialogus in Clinical Neuroscience, 8, 367-381. https://doi.org/10.31887/DCNS.2006.8.4/bmcewen
[494] Dhabhar, F.S. (2019) The Power of Positive Stress—A Complementary Commentary. Stress, 22, 526-529. https://doi.org/10.1080/10253890.2019.1634049
[495] Smith, S.M. and Val, W.W. (2006) The Role of Hypothalamic-Pituitary-Adrenal Axis in Neuroendocrine Responses to Stress. Dialogus in Clinical Neuroscience, 8, 383-395. https://doi.org/10.31887/DCNS.2006.8.4/ssmith
[496] Klimes-Dougan, B., Chong, L.S., Samikoglu, A., Thai, M., et al. (2020) Transcendental Meditation and Hypothalamic-Pituitary-Adrenalaxis Functioning: A Pilot, Randomizd Controlled Trial with Young Adults. Stress, 23, 105-115. https://doi.org/10.1080/10253890.2019.1656714
[497] Yamanaka, Y., Motoshima, H. and Uchida, K. (2019) Hypothalamic-Pituitary-Adrenal Axis Differentially Responses to Morning and Evening Psychological Stress in Healthy Subjects. Neuropsychopharmacology Reports, 39, 41-47. https://doi.org/10.1002/npr2.12042
[498] Storm, F.K. (1993) What Happened to Hyperthermia and What Is Its Current Status in Cancer Treatment? Journal of Surgical Oncology, 53, 141-143. https://doi.org/10.1002/jso.2930530302
[499] Nielsen, O.S., Horsman, M. and Overgaard, J. (2001) A Future of Hyperthermia in Cancer Treatment? (Editorial Comment). European Journal of Cancer, 37, 1587-1589. https://doi.org/10.1016/S0959-8049(01)00193-9
[500] van der Zee, J., Vujaskovic, Z., Kondo, M., et al. (2008) The Kadota Fund International Forum 2004-Clinical Group Consensus. International Journal of Hyperthermia, 24, 111-122. https://doi.org/10.1080/02656730801895058
[501] Wust, P. (2019) Physical Rationale about Amplitude Modulated Radiofrequency Hyperthermia. ESHO-2019, Warsaw, 22-24 May 2019.
[502] Wust, P. (2019) Advantages of Amplitude Modulation in the Radiofrequency Hyperthermia. IX. DGHT-Kongress, Berlin, 20-21 September 2019.

In memoriam: Peter Wust, MD, PhD

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Cite this article as:
Mark W. Dewhirst (2022) In memoriam: Peter Wust, MD, PhD, International Journal of Hyperthermia, 39:1, 1170-1171.
https://doi.org/10.1080/02656736.2022.2115872

Oncothermia Journal 32, September 2022: 155 – 157.
www.oncotherm.com/sites/oncotherm/files/2022-09/Dewhirst_In_memoriam_Peter_Wust.pdf

Professor Peter Wust, MD, PhD
July 9, 2022

It is with great sadness and regret that we announce the death of Professor Peter Wust, on 9 July 2022. Dr. Wust was a translational scientist with rare dual training in both Medicine and Biophysics. This training, combined with his clinical training in radiation oncology set him apart from the majority of scientists engaged in hyperthermia research. This training allowed him to establish himself as a thought leader from the very beginning of his engagement in the field.

Dr. Wust published his first paper in the field entitled 'Numerical Approaches to treatment planning in deep RFhyperthermia', in 1989. From the very start of his career in the field, he showed the how blending of physics /engineering with medicine could lead to better equipment performance in the clinic. In this early work, his emphasis on modulating power deposition using phase and amplitude steering set the stage for later major efforts on this subject that continue to today. His critical view of the importance of equipment performance led to quality assurance standards and several important tools for ensuring proper applicator performance. He was among the first scientists to implement MR thermometry into clinical practice.

Dr. Wust looked beyond traditional microwave /RF/and ultrasound for implementation of hyperthermia. Dr. Wust collaborated with Dr. Jordan in the development of clinically viable systems for using inductive heating of ferromagnetic particles as a means to heat tumors. This collaboration led to the conduct of clinical trials for treatment of primary brain tumors and prostate cancer. He conducted some of the first studies using laser induced hyperthermia for treatment of head and neck cancer as well as exploring use of fever range total body hyperthermia in conjunction with radiotherapy for head and neck cancer.

Overall, he conducted clinical trials involving hyperthermia with radiotherapy and/or chemotherapy for several disease sites, including brain tumors, prostate cancer, rectal cancer, cervix cancer, soft tissue sarcomas and head and neck cancer.

In the past 10 years, Professor Wust continued his broadbased view of the field by publishing detailed scholarly reviews on important topics, such as 'Non-thermal effects of radiofrequency electromagnetic fields', published in Scientific Reports in 2020, and 'Neoadjuvant chemotherapy plus radiation versus chemotherapy plus regional hyperthermia in high-grade soft tissue sarcomas: a retrospective comparison' published in the International Journal of Hyperthermia, in 2018.

Dr. Wust published a total of 364 papers in his career, receiving a total of nearly 17,000 citations and an H-index of 59. The most highly cited paper of his career was the 2002 review in Lancet Oncology, entitled 'Hyperthermia in combined treatment of cancer'. This paper was given the 'Hot Topic' designation by Web of Science and has been cited nearly 1400 times. This paper has stood the test of time and is still being quoted today.

In recognition of his scientific contributions to the field, Dr. Wust received many accolades, including receipt of the ESHO-Award at the International Congress of Hyperthermic Oncology in 2000 and served as the Organizing chair for the 16th Annual Meeting of ESHO in Berlin in 2006. He was the Head of the MR/hyperthermia hybrid unit at Charité Universitätsmedizin Berlin from 2001 to 2010. He was widely recognized for his critical views within the field, serving on the Editorial Board of the International Journal of Hyperthermia until the time of his death.

For more than 40 years his wife Carla was at his side. In his humorous and generous way, his helpful and tolerant nature made him a great person and beloved colleague. For many of us he was an important teacher, mentor and friend.

He was a perfect middle between natural sciences and medicine and therefore a definite role model for the future. His open mind and the effortless bow across subject boundaries are recognized by many as key to modern medicine. Dr. Wust's leadership in the field will be sorely missed, but as can be seen by evaluation of his scientific career, his impact will be felt for decades to come.

Five most highly cited publications

Wust et al. Hyperthermia in combined treatment of cancer. Lancet Oncology 2002, 1363 citations. DOI:10.1016/S1470-2045(02)00818-5

Jordan et al. Magnetic fluid hyperthermia (MFH): cancer treatment with AC magnetic field induced excitation of biocompatible superparamagnetic nanoparticles. Journal of Magnetism and Magnetic Materials, 1999, 1178 citations. DOI:10.1016/S0304-8853(99)00088-8

Hildebrant et al. The cellular and molecular basis of hyperthermia. Critical Reviews in Oncology Hematology 2002, 1173 citations. DOI:10.1016/S1040-8428(01)00179-2

Maier-Hauff et al. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. Journal of Neuro-Oncology 2011, 826 citations. DOI:10.1007/s11060-010-0389-0

Jordan et al. Presentation of a new magnetic field therapy system for the treatment of human solid tumors with magnetic fluid hyperthermia. Journal of Magnetism and Magnetic Materials 2001, 563 citations. DOI:10.1016/S0304-8853(00)01239-7

This work was supported by the

Hungarian National Research Development and Innovation Office

KFI grant: 2019-1.1.1-PIACI-KFI-2019-00011

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