Integrating loco-regional hyperthermia into the current oncology practice: A SWOT and TOWS analysis

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Abstract

Moderate hyperthermia at temperatures between 39 and 45°C is a multifaceted therapeutic modality. It is a potent radiosensitizer, interacts favorably with a host of chemotherapeutic agents and with RT enforces immunomodulation akin to "in situ tumor vaccination." By sensitizing hypoxic tumor cells and inhibiting repair of radiotherapy-induced DNA damage, the properties of hyperthermia delivered with photons provides a tumor-selective therapeutic advantage analogous to high LET neutrons, but without normal tissue toxicity. Furthermore, the high LET attributes of hyperthermia thermoradiobiologically enhance low LET protons; thus, proton thermoradiotherapy mimics 12C ion therapy. Hyperthermia with radiotherapy and/or chemotherapy substantially improves therapeutic outcomes without enhancing normal tissue morbidities yielding level I evidence as reported in several randomized clinical trials, systematic reviews and meta-analyses for various tumor sites. Further, hyperthermia along with immune check point inhibitors and DNA damage repair inhibitors could further augment the therapeutic efficacy resulting in synthetic lethality. Besides technological advancements in hyperthermia delivery, complemented by hyperthermia treatment planning, its integration with radiotherapy treatment plans, online thermometry and adherence to quality assurance guidelines have all ensured safe and effective delivery of hyperthermia to the target region. Additionally, hyperthermia induced by magnetic nanoparticles coupled to selective payloads provides a comprehensive tumor-specific theranostic modality akin to "magic (nano)bullets." To get a realistic overview of the strength (S), weakness (W), opportunities (O) and threats (T) of hyperthermia, a SWOT analysis has been undertaken. Additionally, a TOWS analysis categorizes future strategies to facilitate further integration of hyperthermia with the current treatment modalities. These could gainfully accomplish a safe, versatile and cost-effective enhancement of the existing therapeutic armamentarium to improve outcomes in clinical oncology.

Keywords: hyperthermia, radiation therapy, chemotherapy, immunotherapy, radiosensitizer, hyperthermia treatment planning, SWOT analysis, clinical trials
38. ICHS Meeting (Online!)

Integrating loco-regional hyperthermia into current oncology practice: A SWOT and TOWS analysis

2020 update of oncologic thermotherapy activities in EU/CH

Stephan Bodis on behalf of the Swiss Hyperthermia Network (SHN)
5.11.2020

1 strong partner is enough to strengthen oncologic HT/Thermotherapy

Use meeting debates with opinion leaders to promote oncologic HT/Thermotherapy
The future of Oncologic Thermotherapy
is Technology

Niels Kuster

Prof. Niels Kuster is the founder and Director of the Foundation for Research on Information Technologies in Society (IT*IS Foundation) in Zurich, Switzerland, and Associate Professor of the Department of Information Technology and Electrical Engineering at ETH Zurich.

His research covers many aspects of electromagnetics and computational life sciences, and focus, in particular, on the modeling of both internal and external physical factors that affect human physiology. These include electromagnetic fields (e.g. MR safety assessments), tissue heating and cooling (e.g. hyperthermia and ablation), acoustics in biology (e.g. focused ultrasound/pressure waves), biofluid dynamics (e.g. blood flow and aneurysm), biomechanics (e.g. bone, ligaments, and arterial walls), and dynamic tissue models (e.g. nerve models and tumor growth).

Prof. Kuster has published over 700 publications in books, journals, and proceedings on measurement techniques, computational electromagnetics, dosimetry, exposure assessments, and bioexperimentation. He is a long-time member of several standardization bodies and serves as a consultant on exposure safety assessment for governmental agencies around the globe.
The future of Oncologic Thermotherapy is Biology

Jean Bourhis

Jean Bourhis

Prof. Bourhis has been Chairman of the Radiation Oncology at the Institute Gustave Roussy (Villejuif, France), one of the most prominent Cancer Center in Europe, and moved in 2012 to the CHUV as Head of Radiation Oncology.

His clinical activity is focused on Radiation Oncology Head and Neck cancers, he is chairman of the GORTEC, a cooperative group dedicated to Head and Neck Oncology.

Prof. Bourhis has been for 15 years also Director of a laboratory dedicated to Translational Research in Radiation Oncology. He authored more than 300 scientific papers.

Prof. Bourhis is also Past President of the European Society for Radiotherapy and Oncology (ESTRO), Past President of the ESTRO Cancer Foundation and currently serves as SASRO President.”
Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses

Koby R. Datta, Petra Rüegg, Marco Creaser, Udo S. Gajsi, and Stephen Bodi

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Hyperthermia

Strengths
1. Tumor selective multifaceted modality
   i. Potent radiosensitizer
   ii. Chemosensitizer
   iii. Enhances 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

Weakness
1. Uncertainty in actual 3D temperature distributions
2. Insufficient quality assurance for hyperthermia treatment delivery and monitoring along with inappropriate sample sizes and mid 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

Opportunities
1. Multicentric phase III clinical trials, especially with positive intent and organ preservation
2. Technological development and quality assurance to improve therapeutic outcomes
3. Combining hyperthermia with immune checkpoint and DNA repair inhibition
4. Combining hyperthermia with proteins and use of MAs in urology (colon/breast)

Threats
1. True potential of hyperthermia may remain unexplored in clinical oncology care
2. A cost-effective and safe modality may fall into disuse

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

Heating technology for all body locations

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Frontiers in Oncology 2020
**Clinical evidence hyperthermia**

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<th>Reference</th>
<th>Treatment</th>
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**Strengths**

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All clinical studies report no relevant increase of side effects

re-R+HT: Standard of care for recurrent tumors in several European Countries
**Strengths**

1. Tumor selective, multifaceted modality
   - i. Potent radiosensitizer
   - ii. Chemosensitizer
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**Clinical evidence hyperthermia**

>27 positive randomised trials RT or CT ± HT

**Radiotherapy**

- vd Zee et al. Franckena et al. Dutch Deep Hyperthermia Trial RT+HT in LACC: long term follow-up
- Issels et al. NAC+HRT: Long-term Outcomes Localized High-Risk Soft Tissue Sarcoma

**Chemotherapy**

- Van Diel et al. Hyperthermic Intraoperative Chemotherapy in Ovarian Cancer

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**Review Hyperthermia, Datta et al**

**Clinical evidence hyperthermia**

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**Radiotherapy**

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**Chemotherapy**

- Issels et al. NAC+HRT: Long-term Outcomes Localized High-Risk Soft Tissue Sarcoma

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RT+HT regular care in NL, CH for patients with locally advanced cervical cancer refractory to chemo-radiation

July 2018 Every German Sarcoma cancer centre must provide access to hyperthermia

Jan 2018 Reimbursed in NL for abdominal metastasized Ovarian ca.
Systematic Review and Network Meta-Analysis of Randomized Clinical Trials Locally Advanced Cervical Cancer

59 RCTs in LACC
9894 patients evaluated

Datta et al., Int. J. Radiation Oncology Biology Physics, 2019
ESHO and Atzelsberg Circle combine efforts for CT-RT trials including hyperthermia (HT). Kick-off in Amsterdam 11-2019

**Evaluating**
- Natl. phase II study RT+HT in rectum cancer Germany
- Int. study CT+HT: HEAT trial in pancreatic tumors Germany, Poland

**Running**
- Int. study RT+HT in anal cancer Germany, Italy, CH
- Natl. phase II study CRT+HT inop Rectum Ca. Germany
- Natl. study HyperThermia Enhanced Trabectedin for STS

**Initiatives**
- Int. study proton+HT in sacral chordoma patients CH, Netherlands, USA
- Intl. study RT/CT-HT for muscle invasive bladder cancer
- Natl. RTCT-HT for local advanced non metastatic pancreatic cancer (HEATPAC)

Exclusive company initiated clinical trials.
Reimbursement hyperthermia

Netherlands: HT reimbursed with radiotherapy.
Regional deep and superficial hyperthermia, from January 3rd 2019 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.

Summary

1. Recent Phase III trials confirm the potential of Hyperthermia to boost effectiveness of Radiotherapy and Chemotherapy
2. New multicentric intl. phase III trials are mandatory to keep up to momentum. Sites could be stratified for technology used. Central QA mandatory.
3. Reimbursement of hyperthermia is improving. A long way to go...
4. Innovation is needed to improve workflow for all staff (patients, physicians, physicist, RTT) and to therapy algorithm (prescription, planning, execution, QA) for HT combined with RT/CT
5. Quality assurance is essential for good clinical practice of all devices
Oncologic Thermotherapy/Hyperthermia 2020

Selected Swiss Activities

Reimbursement of Oncologic Hyperthermia (HT combined with RT) in CH
2020: 4 indications for superf. HT approved 2016, 7 for deep HT final approval pending

Dr. med. Felix Gurtner, MD
Facharzt für Strahlentherapie und Strahlentherapiehilfswissenschaften
Kantonsspital Aarau
Schwarzwaldstrasse 657, CH-5000 Aarau
Tel: +41 44 874 4000
Fax: +41 44 874 3000
Official website: www.asa.aarau.ch
ISO-Certification DIN EN ISO 9001:2015 of our Hyperthermia Unit in 2020
(Radiation Oncology Center Aarau and Baden)
Increased acceptance of HT at least by hospital administrators and QA management

SHN/SHRN activities with partners in intl. networks

Workshop ESHO 2019: Strengthen the ESHO clinical trial committee
Intl. clinical study projects development for Hyperthermia combined with Radiotherapy
- F/u meeting in Amsterdam 11/2019 with a voting on presented clinical protocols (active, finalised not yet activated, in development) for phase I/II/III clinical trials
- Joint ESHO/Atzelsberg effort: Launch/conduct intl. multicentric trials in oncologic HT combined with RT and/or CT

EU Horizon 2020 Grant H2020-MSCA-ITN-2020-955625
Research and Innovation Framework Programme
Hyperthermia boosting the effect of radiotherapy
Swiss members: RAO KSA-KSB and ZHAW

ESTRO 2021
Scientific session: Current status of hyperthermia in radiation oncology
Interdisciplinary Symposium on Oncologic Hyperthermia as plenary session jointly with opinion leaders from Japan and USA
ESTRO 2021: ESTRO - JASTRO Hyperthermia Symposium

Biological rational for combining heat and radiation
Jens Overgaard DK

Clinical heating techniques, thermometry and quality assurance
Hans Creeze NL

Status of clinicial Hyperthermia in Japan
Hideyuki Sakurai Jp

Thermoradiotherapy: Clinical evidence and potential indications
Zeljko Vujaskovic USA

Conclusions
Ben Slotman NL

Chairs: Naojuki Shimegatsu Jp and Stephan Bodis CH
HYPERBOOST
Hyperthermia boosting the effect of Radiotherapy
H2020-MSCA-ITN-2020-955625

6 countries
11 beneficiaries
14 PhD students
Budget: € 3,761,881.56

Project coordination:
Hans Crezee
Amsterdam UMC

B2 Århus University
B1 Amsterdam UMC
B10 EMC Rotterdam
B3 RAO KSASKB Aarau
B5 ZHAW Zurich
B7 Medlogix Rome
B9 Chalmers Göteborg
B8 Charité Berlin
B11 MDC Berlin
B4 UKER Erlangen
B6 Sennewald Munich

EU Horizon 2020 Programme
Grant approved for Hyperthermia
Key objectives “HYPERBOOST”

- Train and equip early stage researchers with transferable, multi-disciplinary skills essential in high-end biomedical engineering, clinical hyperthermia and translational oncology (WP2)
- Obtain and validate new insights into clinical working mechanisms of hyperthermia (WP3)
- Translate preclinical and clinical results (WP3, WP5) into mathematical relations and treatment planning models (WP4)
- Apply novel treatment planning models for personalised treatment (WP4) clinically to improve the efficacy of clinical treatments (WP5)
- Initiate, stimulate and profit from multidisciplinary cross-pollination between the disciplines involved in hyperthermic oncology (WP3-5)
- Consolidate and expand the European infrastructure and industry for hyperthermia research and clinical application (WP 2-6)