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Letter to the editor

Because of the low quality evidence, hyperthermia cannot be included in the benefit catalogue for oncologic indications

Strong commercial interests are presumed behind the editorial of R. Sauer et al.

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Aufgrund der Evidenz von geringer Qualität kann Hyperthermie nicht in den Leistungskatalog für onkologische Indikationen aufgenommen werden

Vermutung starker kommerzieller Interessen hinter dem Editorial von R. Sauer et al.

Original publication

Sauer R, Creeze H, Hulshof M et al (2012) Concerning the final report “Hyperthermia: a systematic review” of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. *Strahlenther Onkol* 188(3):209–215

Letter to the editor

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We are responding to the editorial from Sauer et al. [1]. In the editorial, the evidence analysis of the Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)—an academic institution—on hyperthermia was severely criticised. We are disappointed that the authors did not contact us or write us about the editorial: It is indeed very unusual *not* to write a letter to the authors (at least concurrently), but to publish an editorial on the HTA report [2] without contacting either the institution or the authors of the systematic review in question beforehand. In (mis-)using the role of the editor-in-chief, this fact gives the impression that the authors of the editorial do not wish to initiate a scientific debate about methodology, but to openly question an institution, namely the LBI-HTA. We express our grave concerns that the editorialist R. Sauer, Head of the Department of Radiooncology in Erlangen, has written this open letter not in his role as editor-in-chief, but as a speaker of the so-called “Atzelsberg Circle”, whose members are all providers of hyperthermia in Germany.

Hyperthermia is—most often—being delivered by the devices of the BSD Medical Corporation, Salt Lake City/NASDAQ listed: BSD-500, 2000, 2000-3D, 2000-3D/MR. BSD-500 has received U.S. Food and Drug Administration (FDA) approval for the treatment of certain tumors, while BSD-2000 does not concurrently have FDA approval except as an *investigational device*, although it has obtained HUD/Humanitarian Use Device designation for use in conjunction with radiation therapy for the treatment of cervical carcinoma patients [3][4] for demonstrating the product’s safety and *probable* benefit for the treatment of a disease. In the US where the devices are produced, the two more advanced devices, BSD 2000-3D and 2000-3D/MR, have not been approved by the FDA at all for *any kind of use* within the USA.

Nevertheless, the BSD products have obtained CE-mark certifications necessary for marketing in Europe. Hyperthermia with BSD is being carried out in five to six European countries only [5], with the highest geographical concentration in Germany (in nine centers) and the Netherlands (three centers), while in many other countries only one device per country is installed—presumably for research reasons, since they are almost all located in university settings.

European research institutions for hyperthermia are

- Daniel den Hoed Cancer Center of the Academisch Ziekenhuis (Rotterdam, the Netherlands),
- Haukeland University Hospital (Bergen, Norway),
- Dusseldorf University Medical School, Tübingen University Medical School, Essen University Hospital, Charité Medical School of Humboldt University (Berlin), Luebeck University Medical School, Munich University Medical School Grosshadern, Interne Klinik Argirov of the Munich Comprehensive Cancer Center, University of Erlangen (all in Germany),
- University of Verona Medical Center (Italy),
- Graz University Medical School (Austria, no more since 2010),
- Kantonsspital Aarau (Switzerland).

May we firstly refer to the current evidence base: Hyperthermia has been “on the scene” for 25 years: Clinical trials were mostly carried out in the late 1980s and mid-1990s [6] in various cancers. Because of double and triple publications on the same patients (as it is done quite

often in medicine), at first sight the field of hyperthermia looks somewhat researched. Taking a second look (excluding double publications), it is different: After the publication of the LBI-HTA report in early 2010 [2], only one Phase III multi-centric trial was published by Issels in 2010 [7], who is a provider of hyperthermia and an owner of BSD stocks (CoI Statement 2007 [8]). Between 1987 and 2010, altogether 11 RCTs were published on the following four cancer indications:

- cervix (Sharma 1989, van der Zee 2000, Harima 2001, Vasanthan 2005, Franckena 2008). Two RCTs were not taken into consideration: one 3-page paper on a RCT is in Chinese language/abstract only in English (Chen 1997), another (Datta 1987) is not listed in Medline, and is neither available in the British Library (BL Direct) nor via three different libraries in Subito (but astonishingly often cited within hyperthermia publications),
- breast (Vernon 1996, Jones 2005),
- bladder (van der Zee 2000, Colombo 2003) and
- sarcoma (no RCT until early 2010, now Issels 2010).

Currently one more major trial is listed in the controlled clinical trials registry (www.clinicaltrials.gov) as recruiting (366 patients with pancreas cancer): the Hyperthermia European Adjuvant Trial (HEAT), with Issels as the primary investigator.

We respect enthusiastic scientists and clinicians, but the evidence for new interventions have to be considered carefully before new interventions become standard practice. We are concerned about the small group of scientists and clinicians researching on hyperthermia and the deep involvement of the producer in all the meetings. Unfortunately, hyperthermia providers, primary investigators/researchers, and even authors of review publications [9] [10] are all the same experts, and it proves difficult to find independent publications. At the ESTRO Lunch Symposium 2012 on Hyperthermia and Radiation: Progress in Targeted Tumor Therapy (sponsored by Senewald Medizintechnik—a major shareholder in BSD Med. Corp. and stockholder of BSD), three out of the five speakers are members of the Atzelsberg Circle and two from the Dutch (Rotterdam) centre, all of them working with BSD products. In none of the published studies from the respective authors of clinical research with BSD products is a conflict of interest statement declared.

Although hyperthermia is being carried out in some clinics in the US and Europe (and China), in the NCCN/National Comprehensive Cancer Network Evidence-Based Guidelines

(update 2012) hyperthermia is mentioned (but not recommended) only as an option for consideration for two indications (out of the 11 indications under review), namely breast cancer and soft tissue sarcoma cancer.

For breast cancer, the NCCN Guidelines say [11]

The Guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3). There have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences. While there is heterogeneity among the study results, a series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone. No differences in overall survival have been demonstrated.

For sarcoma, the NCCN Guidelines say [11]

The results of a recent phase III randomized trial (EORTC 62961) showed that regional hyperthermia (RHT) increases the benefit of neoadjuvant chemotherapy in patients with localized high-risk STS. In this study, 341 patients were randomized to receive either neoadjuvant chemotherapy with etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with RHT (EIA plus RHT). After a median follow-up of 34 months, among 149 patients with extremity sarcoma, the 2-year DFS and local PFS rates were 70 and 92% respectively for patients treated with EIA plus RHT. The corresponding survival rates were 57 and 80% for those treated with EIA alone. However, these results need to be confirmed in large cohort studies and the use of RHT with preoperative chemotherapy is not recommended in the guidelines.

The NCI still writes [12]

A number of challenges must be overcome before hyperthermia can be considered a standard treatment for cancer. Many clinical trials are being conducted to evaluate the effectiveness of hyperthermia. Some trials continue to research hyperthermia in combination with other therapies for the treatment of different cancers. Other studies focus on improving hyperthermia techniques.

Hyperthermia in oncology is obviously not considered standard practice (yet).

We would like to respond to the criticism on methodology, raised in the editorial, in more detail: The authors of the editorial (the Atzelberg Circle of the German Cancer Society) mainly criticize that our (LBI-HTA) report on hyperthermia was based on the 2005 published G-BA report [6] on the same interventions, not ourselves considering the published trials before 2005 again. Our response: In an era of ever increasing numbers of not only original/primary medical research, but also of secondary analyses/systematic reviews [13], the building of one's own evidence synthesis upon existent high quality reviews with an identical research question is a common and methodically accepted practice among HTA-/EbM or health care regulatory institutes. The prerequisite is a scientifically rigorous review from credible institutions (credibility is based on transparent methods of searching and extracting data from clinical trials) [14]. By criticizing our HTA report, the authors of the editorial implicitly question the G-BA report and its scientific rigour.

To summarize: all RCTs available in German or English language until mid-2005 have been included and considered in the G-BA report [6], all RCTs available in German or English language published between 2005 and January 2010 were included in our LBI-HTA report on hyperthermia [2]. Other publications [7][10][15] had not been published at the time our report was released and could therefore not be considered. Besides the fact that the “best available evidence” (RCTs) was considered, many further references, such as observational not-controlled studies, were included as additional supporting material. It is therefore of great astonishment to us that our approach that follows the standard principles of evidence-based medicine has been criticised as “subjective, selective and flawed in parts”.

The methodology we applied was a systematic review (in contrast to a selective review): In systematic reviews, literature is systematically searched for in several databases (Medline, EmBase, Cochrane), literature is in-/excluded along pre-defined criteria, data (patient-relevant endpoints and safety data) are extracted. All work steps are carried out and controlled by two independent researchers. In contrast, in (traditional) narrative reviews only selected literature—mostly to support one's own hypothesis—is cited. We follow the standards of systematic reviews in all our evidence analyses strictly.

In 2005 the G-BA decided, because of the low quality evidence, not to include hyperthermia in the German benefit catalogue for any of the 11 indications [16]. Similar to Germany, Austrian decision-makers decided in 2010, based on the LBI-HTA report, not to

invest in hyperthermia again, owing to the lack of convincing evidence. Interestingly, possibly because of the regulatory decisions in Germany (much later in Austria) *not* to reimburse hyperthermia, the stocks of BSD fell dramatically between 2007 and 2010 [17]. Since strong commercial interests have to be presumed behind this very unusual way of writing an editorial without contacting the authors first, we ask for disclosure of CoI/conflict of interest statements (consultancy honoraria, research grants, shareholder interests from BSD or any other hyperthermia supplier, income from privately insured patients, etc., see [18][19]), as it is common practice in international journals for the authors as much as for editorialists.

An update of the LBI-HTA report from 2010 is being carried out and will be published within the next few months.

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References

1. Sauer R, Creeze H, Hulshof M et al (2012) Concerning the final report “Hyperthermia: a systematic review” of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. *Strahlenther Onkol* 188(3):209–215
2. Mathis S, Johansson T (2010) Hyperthermie. In: Decision Support Document. Ludwig Boltzmann Institut für HTA. http://eprints.hta.lbg.ac.at/883/1/DSD_36.pdf. Accessed 23 July 2012
3. United States Securities and Exchange Commission (2011) Investors information on BSD Medical Corporation. http://www.bsdmedical.com/~bsdmedic/files/fillings/16-BSD_Medical_Form_10-Q_2-28-11.pdf. Accessed 23 July 2012
4. Stomp W (2011) BSD-2000 Hyperthermia System Receives FDA HDE Marketing Approval. *Medgadget*, <http://medgadget.com/2011/11/bsd-2000-hyperthermia-system-receives-fda-hde-marketing-approval.html>. Accessed 23 July 2012
5. BSD Medical Corporation. BSD-Providers. http://www.e-factoryatwork.com/teamwork-new/bsdpro/treatment_providers.html. Accessed 23 July 2012

6. G-BA/Gemeinsamer Bundesausschuss, Hyperthermie (2005) Zusammenfassender Bericht des Unterausschusses “Ärztliche Behandlung” des Gemeinsamen Bundesausschusses über die Bewertung gemäß § 135 Abs. 1 SGB V der Hyperthermie (u. a. Ganzkörper-Hyperthermie, Regionale Tiefenhyperthermie, Oberflächen-Hyperthermie, Hyperthermie in Kombination mit Radiatio und/oder Chemotherapie). G-BA/Gemeinsamer Bundesausschuss: Siegburg. <http://www.g-ba.de/downloads/40-268-236/2005-06-15-BUB-Hyperthermie.pdf>. Accessed 23 July 2012
7. Issels RD, Lindner LH, Verweij J et al (2010) Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* 11(6):561–570
8. Issels RD, Lindner et al (2007) Regional hyperthermia (RHT) improves response and survival when combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas (STS) of the extremities, the body wall and the abdomen: a phase III randomised pros. *J Clin Oncol (ASCO Annual Meeting Proceedings (Post-Meeting Edition))*. 25(18 S (June 20 Supplement)):10009)
9. Falk MH, Issels RD (2001) Hyperthermia in oncology. *Int J Hyperthermia* 17(1):1–18
10. Lutgens L, Zee J van der et al (2010) Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* 3:39
11. NCCN/National Comprehensive Cancer Network (2012) National Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/pdf. Accessed 23 July 2012
12. NCI/National Cancer Institute. Hyperthermia in cancer treatment. <http://www.cancer.gov/cancertopics/factsheet/Therapy/hyperthermia>. Accessed 23 July 2012
13. Booth A, Clarke et al (2011) An international registry of systematic-review protocols. *Lancet* 377:108–109
14. LBI-HTA (2009) (2. Aufl.) Internes Manual. Abläufe und Methoden. [http://eprints.hta.lbg.ac.at/713/3/HTA-Projektbericht_06_\(2.Auflage\).pdf](http://eprints.hta.lbg.ac.at/713/3/HTA-Projektbericht_06_(2.Auflage).pdf). Accessed 23 July 2012
15. Colombo R, Salonia A et al (2010) Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int* 107(6):912–918
16. Bundesanzeiger (2005) Bekanntmachung [1429 A] eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Anlage B “Nicht anerkannte

- Untersuchungs- und Behandlungsmethoden” der Richtlinie zur Bewertung medizinischer Untersuchungs- und Behandlungsmethoden (BUB-Richtlinie), Bundesministerium für Gesundheit und Soziale Sicherung, Editor. BAnz. p. 7485. <http://www.g-ba.de/downloads/39-261-199/2005-01-18-BUB-Hyperthermie.pdf>. Accessed 23 July 2012
- 17.Financen.net. BSD Medical Aktie. http://www.financen.net/kurse/kurse_historisch.asp?pkAktieNr=23438&strBoerse=XETRA&pkZeit=50000. Accessed 23 July 2012
- 18.IQWIG/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (2012) Interessenskonflikte. <https://www.iqwig.de/index.924.html>. Accessed 23 July 2012
- 19.Lieb K, Klemperer D, Ludwig WD (2011) Interessenkonflikte in der Medizin, 1st edn., Springer, Heidelberg (vol 8)

Authors' reply

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The response of Dr. Wild of the Ludwig Boltzmann Institute of Health Technology Assessment to the editorial from R. Sauer et al. [1] in *Strahlentherapie und Onkologie* 2012, “Concerning the final report “Hyperthermia: a systematic review” of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010 [2], is unnecessarily polarizing to the discussion on whether or not hyperthermia is evidence based.

The strategy that Dr. Wild appears to have employed is

- first distract the reader from the scientific argument by claiming the other party has treated you impolitely,
- next add some biased additional information to support your case again, and
- finally, end by accusing the other party of foul play.

We have decided not to follow the same strategy, but give honest responses to the issues raised by Dr. Wild.

¹ R. Sauer and H. Crezee contributed equally to this manuscript.

The first question is whether Dr. Wild should have expected the authors to contact or write to Dr. Wild privately in response to the public report

If we review this premise from a distance, it is clear that the Ludwig Boltzmann Institute consciously made the decision to make their report publically available. Any public organization must know that when they publish a report, there is a substantial risk, and even an assumption, that individuals or groups will respond publicly if they strongly disagree with the content and the conclusions of the report. Publication of a scientific disagreement has nothing to do with misusing someone's position as an editor. In fact it is his option, as well as his scientific duty, to be critical to institutional reports and, if needed, to make his concerns public through an editorial. Scientific disagreements with published reports must be submitted publicly in order to provide the medical community with the opposing conclusions. If the authors of the HTA report would have submitted their report for publication to *Strahlentherapie und Onkologie*, their complaint may have been justified. However, it is just a public response to a public report.

The accusation by Dr. Wild that the authors of the editorial do not wish to initiate a scientific debate about methodology is definitely not correct. On the contrary: publically challenging the conclusion of the report is exactly the scientific debate Dr. Wild is asking for. In the entire editorial, the authority of the LBI-HTA was never questioned; what was questioned is whether the procedure followed by the LBI-HTA in this specific report is correct and scientifically valid. The essential point of the editorial was that there were good and valid reasons to question the procedure followed by the LBI-HTA.

The second question concerns the comments in the editorial on the robustness of the systematic review that was performed by the LBI-HTA

In contrast to Dr. Wild's statement, "the building of one's own evidence synthesis upon existent high quality reviews with an identical research question is a common and methodically accepted practice among HTA-/EbM or health care regulatory institutes", the requirements for a high quality systemic review, as stated by the independent Prisma group [3] are quite clear:

*A systematic review attempts to collate **all** empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a systematic review are: (a) a clearly stated set of objectives with an explicit, reproducible methodology; (b) a systematic search that attempts to identify all studies that would meet the eligibility criteria; (c) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and (d) systematic presentation, and synthesis, of the characteristics and findings of the included studies.*

By including the GB-A report instead of including all of the studies, the LBI-HTA report is no longer fulfilling the basic criteria of a systematic review. Key in any systemic review is the assessment of the quality of the randomized clinical trials (RCT) included in the systematic review by the authors, which provides an assessment of the efforts taken to avoid bias. It is unclear from the LBI-HTA report how the authors guaranteed that the selection criteria in the LBI-HTA study was identical to the GB-A report, particularly as the persons evaluating these criteria were not the same.

Further, in order to prevent bias and adequately judge the quality of the randomized trials, we quote the Consort Group [4] who explicitly indicated that

Nonpharmacologic trials usually test complex interventions involving several components. Such treatments are consequently difficult to describe, standardize, reproduce, and administer consistently to all patients. All of these variations could have an important impact on the estimate of the treatment effect.

In this respect it is noteworthy that the quality of the hyperthermia treatment delivered as part of the RCT has not been given more impact on the interpretation of the value of the study, e.g., the “Vasanthan et al.” RCT study.

Reimbursement status of hyperthermia in other countries

It is interesting to note that the conclusions of the LBI-HTA report and GB-A report are in great contrast to the conclusion of other equally highly recognized health authorities of the Netherlands² and Switzerland³.

² Health Council of the Netherlands, Health Insurance of the Netherlands.

Hyperthermia is presently reimbursed in a growing number of countries. The editorial mentioned the NCCN and the Dutch guidelines regarding breast cancer. Dr. Wild cites the NCCN guidelines which propose consideration of the addition of hyperthermia to irradiation, but also mention the convincing, statistically significant increase in local tumor response when hyperthermia is added to radiotherapy. Note that hyperthermia treatment for breast cancer is reimbursed in the U.S., as well as in Switzerland and the Netherlands. The Dutch guidelines listed on <http://www.oncoline.nl>, not mentioned by Dr. Wild, give a more firm recommendation for the use of hyperthermia and low dose re-irradiation for recurrent breast cancer in previously irradiated areas. Both the latest version of 13 February 2012, and earlier versions as far back as 2008 state that hyperthermia is the treatment of choice ('behandeling van keuze') for this indication. Also note that hyperthermia is reimbursed and standard practice for this tumor indication in the Netherlands. Hyperthermia is also reimbursed and considered to be standard practice by the Swiss health authorities. Note that these Swiss, Dutch and other guidelines are based on the same standard principles of evidence-based medicine used by the LBI-HTA report, yet reach opposite conclusions concerning the use of hyperthermia, based on the same available clinical evidence.

The same standard principles of evidence-based medicine recently led to reimbursement for the application of hyperthermia for locally advanced cervical cancer in Switzerland and in the Netherlands, again contrary to the conclusions of the LBI-HTA. Finally, the extensive financial support for hyperthermia research by the official Cancer Societies in many countries (e.g., KWF Dutch Cancer Society/Queen Wilhelmina Cancer Foundation, the Netherlands; DKG German Cancer Society, DFG German Research Foundation, Deutsche Krebshilfe e.V. [“German Cancer Aid”], Germany) is another testimony of the official endorsement of the scientific basis of clinical hyperthermia.

Allegations to the authors and Atzelsberg Circle members

A major concern for Dr. Wild is the perceived dominant role of the manufacturer Sennewald Medizintechnik/BSD Med. Corp. in the field of hyperthermia and the potential financial relationship of the authors and Atzelsberg Circle members with this company. In response to this serious, unsupported, and malicious allegation, we would like to state that the purpose of a conflict of interest statement is precisely to reveal such a conflict of interest. This is

³ TARMED Suisse.

precisely what Dr. Issels has done; he has always informed the world and, equally important, the co-authors of his papers on the fact that he holds a handful of shares in BSD Medical. Note that “Lancet Oncology” chose to exclude this extremely minor ownership in the conflict of interest statement for the sarcoma study. We followed the standard procedure by reviewing the individual disclosures, which resulted in all authors declaring that there is no conflict of interest. In fact, only one out of the five authors of the original Editorial has a connection to BSD and two out of five authors do not even use BSD equipment. More importantly, the relevant clinical papers for the four cancer indications discussed in the editorial and deemed admissible by Dr. Wild are clearly independent and unbiased (see below).

- Cervix. Five papers are deemed admissible by Dr. Wild. The study of Sharma et al. [5] was conducted using an intracavitary hyperthermia applicator. The studies of van der Zee et al. [6] and Franckena et al. [7] were conducted with various devices with about half of the patients treated with the BSD-2000 system and a similar number with the AMC-4 deep heating device. The studies of Harima et al. [8] and Vasanthan et al. [9] were conducted using the Thermotron RF-8 (Yamamoto Vinita Co, Osaka, Japan).
- Breast cancer. The majority of the 171 patients receiving hyperthermia in the study of Vernon et al. [10] were treated with various devices, mostly operating at 434 MHz. Only the 17 patients receiving hyperthermia at the Princess Margaret Hospital were treated at 915 MHz, possibly with BSD equipment. The study of Jones et al. [11] was performed using spiral microstrip applicators designed at Duke.
- Bladder. The study of van der Zee et al. [6] was conducted with various devices, with about half of the patients treated with the BSD-2000 system and a similar number with the AMC-4 deep heating device. The study by Colombo et al. [12] was conducted with an intracavitary microwave antenna system (Synergo, Amstelveen, The Netherlands).
- Sarcoma. The patients in the Issels et al. [13] paper were treated with the BSD-2000 system.

Thus, only one out of the nine RCTs deemed admissible by Dr. Wild was performed with BSD equipment; two studies were performed for 50% if the patients treated with BSD equipment; and the remaining six studies were performed with non-BSD hyperthermia equipment. There are a total of 74 authors involved with the RCTs. Sixty-seven out of 74 appear only once, four appear two times and three authors appear three times. There is no

repetition in authors in the two breast cancer trials or in the two bladder cancer trials. There is no repetition in the authors for the five cervical cancer trials, with exception of the van der Zee et al. [6] and Franckena et al. [7] studies. Thus, contrary to concerns expressed by Dr. Wild, there is little duplication in author names in this set of nine publications, and few of the studies used BSD equipment. Therefore, there is no indication of a dominant role of BSD/Sennewald in the relevant clinical papers, contradicting the claims that it is difficult to find independent publications.

Basic interest of the Atzelsberg Circle members

Clearly, the driving force for all participants of the Atzelsberg Circle is first their genuine interest in the benefit of the patient combined with their scientific interest in establishing the potential benefit of hyperthermia. None of the Atzelsberg Circle members, medical doctors and other health care professionals would treat patients with hyperthermia if hyperthermia were of were no benefit (either cure or improved quality of live) for the patient. This group of motivated and committed scientists and clinicians are not driven by commercial interests.

In our opinion, there are simply no other viable options than low dose re-irradiation combined with hyperthermia for certain tumors, e.g., recurrent breast cancer. We note that the health authorities in many countries have decided to reimburse hyperthermia based on the rigorous application of evidence-based medicine for a number of tumor indications. Our disagreement with Dr. Wild is clearly based on differences in the interpretation of the available clinical evidence and it is good to hear that the announced update of the LBI-HTA report will include more recent papers, including the papers by Issels et al. [13], Lutgens et al. [14], and Colombo et al. [12, 15]. However, we do expect the LBI-HTA to conduct a genuine systematic review, including meta-analysis, Forest plots, etc. The systematic review must also include an independent evaluation by qualified hyperthermia physicists of the quality of the hyperthermia treatments delivered for the studies.

The unsupported and malicious attack by Dr. Wild on the integrity of the researchers and the Atzelsberg Circle members who disagree with the methodology employed in the review conducted by LBI-HTA is not appropriate for a scientific evaluation of a medical treatment. A scientific evaluation of medical treatments requires an open dialog and objective discussions based on scientific methodology. Personal attacks are not only inappropriate; they also hinder the objective evaluation required to arrive at correct conclusions.

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References

1. Sauer R, Creeze H, Hulshof M et al (2012) on behalf of the Interdisciplinary Working Group for Clinical Hyperthermia (Atzelsberg Circle) of the German Cancer Society and the German Society of Radiooncology. Concerning the final report “Hyperthermia: a systematic review” of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010”, *Strahlenther Onkol*:1–4
2. Mathis S, Johnsson T (2010) Hyperthermie. Decision Support Document 36 (2010); Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA) ISSN-online: 1992–0496, available at <http://eprints.hta.lbg.ac.at>. Accessed 27 Jan 2012
3. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Medicine* 6(7):e1000100 (<http://www.plosmedicine.org>)
4. Boutron I, Moher D, Altman DG et al (2008) Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 148:295–309
5. Sharma S, Patel FD, Sandhu APS, Gupta BD, Yadav NS (1989) A prospective randomised study of local hyperthermia as a supplement and radiosensitizer in the treatment of carcinoma of the cervix with radiotherapy. *Endocuriether/Hyperthermia Oncol* 5:151–159
6. Zee J van der, Gonzalez GD, Rhoon GC van et al (2000) Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a

- prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet* 355(9210):1119–1125
7. Franckena M, Stalpers LJ, Koper PC et al (2008) 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* 70(4):1176–1182
 8. Harima Y, Nagata K, Harima K et al (2001) A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *Int J Hyperthermia* 17(2):97–105
 9. Vasanthan A, Mitsumori M, Park JH et al (2005) Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the international atomic energy agency. *Int J Radiat Oncol Biol Phys* 61(1):145–153
 10. Vernon CC, Hand JW, Field SB et al (1996) Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* 35(4):731–744
 11. Jones EL, Oleson JR, Prosnitz LR et al (2005) Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 23(13):3079–3085
 12. Colombo R, Da Pozzo LF, Salonia A et al (2003) Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J Clin Oncol* 21(23):4270–4276
 13. Issels RD, Lindner LH, Verweij J et al (2010) Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* 11(6):561–570
 14. Lutgens L, Zee J van der, Pijls-Johannesma M et al (2010) Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* 3
 15. Colombo R, Salonia A, Leib Z et al (2011) Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int* 107(6):912–918