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Concerning the final report "Hyperthermia: a systematic review" of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010

The "Final Report" from the Ludwig Boltzmann Institute Vienna (LBI), described as the result of a "systematic review", takes the report published in 2005 by the German Joint Federal Committee (JFC Report) [1]—the most senior decision-making body for healthcare politics in Germany—and assesses whether evidence has changed for the 11 oncological indicators for hyperthermia (HT) that were classified as promising since the latter was published. The authors state that they also conducted other reviews of the literature in medical databases and in Health Technology Assessment databases [2].

The LBI authors conclude by stating that no general application of any of the forms of hyperthermia treatment can currently be recommended for any of the tumor indications considered. The authors state that existing evidence from studies is insufficient to demonstrate a net benefit for the interventions evaluated. Accordingly, the application of hyperthermia should take place exclusively within the scope of clinical trials.

The Ludwig Boltzmann Institute Vienna (LBI) bases its findings solidly on the German JFC Report, which rejects any net benefit for cancer patients from hyperthermia in the temperature range 41–45°C. However, the LBI report only considers relevant publications from PubMed published between 2005 and 2009. If literature reviews are based on only a limited period of time, then there is a danger that, while no evidence exists in the limited period itself, evidence is in fact present if one considers the total period of available time. This appears to be the case for hyperthermia therapy.

Rejoinder

The "Atzelsberg Circle" is an interdisciplinary working group of clinicians and basic research scientists drawn from the German Cancer Society ("Deutsche Krebsgesellschaft e. V.", DKG) and the German Radiotherapy Society ("Deutsche Gesellschaft für Radioonkologie e. V.", DEGRO). This Group, which conducts research on the clinical application of hyperthermia in the form of prospective clinical trials, rejects outright the conclusions drawn by the LBI. The literature review itself was conducted thoroughly, yet the interpretation of the results appears to be subjective, selective, and flawed in parts. Furthermore, for the indications for clinical hyperthermia therapy listed in this publication, conclusive sets of data nonetheless exist (although possibly unavailable to LBI). This material justifies—and even to an extent advocates—the clinical application of local and deep-tissue hyperthermia. In support of this conclusion, we cite four examples of malignant tumors for which conclusive data are supportive of the net benefit of hyperthermia treatment as an adjunct to radiation therapy and chemotherapy. Hyperthermia was used in these treatments to sensitize tumor cells vis-à-vis ionizing radiation or chemotherapeutic agents and have been proven both in assays and in clinical trials.

Breast cancer

Six randomized trials investigated the efficacy of combined radiation therapy and local hyperthermia for female patients with a locally advanced mammary carcinoma or breast cancer recurrence. Five of these trials were conducted between 1988 and 1991 by the UK Medical Research Council, the European Society of Hyperthermic Oncology (ESHO), the Dutch Hyperthermia Group, the Princess Margaret Hospital, and the Ontario Cancer Institute [3]. The patients involved were those for whom primary surgery was deemed unsuitable. In each case, the primary endpoint was the rate of complete cancer remission (CR). Since the rate of cancer patient recruitment was at times sluggish, a decision was made to pool the results into a meta-analysis and to publish the results in a joint paper.

A total of 306 patients were studied: 44% (135/306) received radiation therapy

only, while 56% (171/306) received local hyperthermia in addition to radiotherapy. The biologically effective radiation dose was 40–70 Gy, delivered in single fractions of 1.8–4.0 Gy. According to the corresponding study records, between 2 and 8 hyperthermia treatments were applied to the radiation fractions. Each hyperthermia session lasted 45–70 min. The target temperature in the vicinity of the tumor was 42.5–43.0°C; total treatment time was 2–5 weeks. A total of 41% of patients experienced complete remission after radiation therapy alone; for combined therapy, the figure was 59% ($p < 0.001$). The most pronounced effects from hyperthermia were observed in patients who had received prior radiation therapy to the tumor site, which meant they were unable to receive a full, i.e., assuredly tumoricidal, radiation dose. During the follow-up observation period, a relapse after CR was experienced by 31% of those patients who received radiation therapy alone, but by only 17% of combined therapy patients ($p = 0.007$). However, since most cases (227/306) proceeded to exhibit systematic recurrence outside the hyperthermia-treated region, the improved local control in the hyperthermia-treated group did not also translate to improved overall survival. Local hyperthermia was well tolerated and did not trigger any relevant increased acute or late toxicity, even for patients who had already received a course of radiation therapy.

Results from the sixth trial of hyperthermia in the treatment of breast cancer were published in 2005 and 2007 by Duke University (North Carolina, USA) [4, 5]. A total of 108 patients with various types of cancer were prospectively randomized to receive either radiation therapy alone ($n = 52$) or a simultaneous additional treatment of local hyperthermia ($n = 56$). Of patients treated with radiation therapy, 63% (33/52) had a breast cancer chest wall recurrence, 12% (6/52) had head and neck cancer, 12% (6/52) had a malignant melanoma and 13% (7/52) had other histologies. In the combined group, the distribution was 66% (37/56), 14% (8/56), 9% (5/56), and 11% (6/56), respectively. The median radiation dose for patients who had already received prior radiotherapy was 41 Gy (18–66 Gy); patients who had not received prior radiotherapy received 60 Gy (24–70 Gy). In the HT group, depending on randomization, patients received up to 10 local hyperthermia sessions twice weekly. These sessions lasted 1–2 h each and were delivered at intervals of at least 48 h. The temperature achieved in the target area was measured invasively. The temperatures in the tumor and in the surrounding normal tissue were limited to 43°C and 50°C, respectively. The CR rate was 66% in the HT group and 42% in the control group ($p = 0.02$). There were no significant differences in the systematic therapy for either study group. The improved response in the HT group resulted in significantly improved local tumor control (48% vs. 25%, $p = 0.02$). This effect was most marked in patients who had received prior radiation therapy.

Additional support of efficacy was provided by the qualified analysis of the Dutch working group concerning the application of local hyperthermia to chest wall recurrence in breast cancer [6]. All these data have contributed to the fact that hyperthermia is now explicitly recommended for use in the treatment of locoregional recurrence of breast cancer in guidelines issued by both the US National Comprehensive Cancer Network (NCCN, Version 2–2011 [7]) and in the Dutch National Guidelines (Version 2011 [8]).

Cervical cancer

The results of a sequence of prospectively randomized hyperthermia studies for cervical cancer unmistakably demonstrated the value of hyperthermia as a complementary treatment to radiotherapy [9, 10, 11, 12, 15, 16]. An Indian study [13] cannot be used for analysis at this juncture. This study was heavily criticized since it lacked any form of quality control for the delivery of the hyperthermia therapy (e.g., thermometry, technique). Experts in the field are unanimous in their opinion that the patients simply received insufficient hyperthermia treatment [14].

Notwithstanding the quality deficiencies in this Indian study—as noted above—the Final Report from the Boltzmann Institute in fact bases its argumentation regarding cervical cancer on Vasanthan and coworker's publication in IJROBP [13]. On the other hand, the Dutch Phase III trial on cervical cancer [15]—and its 12-year post-trial observation period [16]—is discounted since it allegedly contributes "nothing new". On the contrary, the Dutch Phase III study not only shows significantly improved locoregional control compared to radiotherapy alone but also a 17% improvement to overall survival. Moreover, the LBI Report also ignores the Cochrane analysis [14]: this paper utilizes meta-analysis to demonstrate a significant positive effect for hyperthermia treatment both on local control and survival when applied in combination with radiation therapy. It is worth pointing out that this analysis also considers the Vasanthan et al. study: while technically inadequate, the Vasanthan study draws a negative conclusion and yet this negative conclusion has not the slightest negative impact on the positive overall result of hyperthermia for cervical cancer [9, 10, 11, 12].

These overall positive results convinced the Dutch health authorities, thus, causing them to categorize hyperthermia as an appropriate standard therapy option for the treatment of cervical cancer. This decision is based on clinical data that were also available in Germany at the time the Final Report was published and which, therefore, should also have been taken into account.

Bladder cancer

Key elements of the use of organ-retention radiochemotherapy (RCT) for the treatment of urinary bladder cancer were developed by the Radiotherapy Clinic at the University of Erlangen [17, 18, 19] [20]. Between 1982 and 2006, 478 patients with T categories T1–4 were treated in a total of four groups. Initially, patients were given radiotherapy alone ($n = 126$); followed by either cisplatin ($n = 145$) or carboplatin ($n = 95$) administered simultaneously for radiation sensitization. Finally, 112 patients received cisplatin and 5-fluorouracil simultaneously with radiation. This approach resulted in complete remission rates of 61%, 66%, 82%, and 88%, respectively. The 5-year overall survival was 40%, 45%, 62%, and 74%, respectively, with bladder retention rates of 37%, 40%,

47%, and 61% respectively—i.e., a noticeable improvement [17, 18, 19, 20]. Unfortunately, many complete remissions do not last. To continue to prohibit local recurrence in the bladder, we began a Phase II trial in 2005 with the aim of testing the effects of adding regional deep-tissue hyperthermia [21]. Initial analyses for 45 patients with T1–2 urinary bladder cancer revealed a significant further improvement in complete remissions. Long-term progress results are not available at this time.

However, two randomized trials on the complementary use of hyperthermia are available: Colombo et al. [22] carried out a randomized study of 83 patients with primary or recurrent Ta-T1 transitional cell carcinoma of the urinary bladder. Treatment consisted of a full TURP followed by either intravesical mitomycin C alone or combined with intravesical hyperthermia. For urinary bladder cancer with an intermediary and elevated risk, hyperthermia lowered the local rate of recurrence after 2 years from 57.5 to 17.1% ($p = 0.0002$). Further, in the well-known Dutch Phase III trial, van der Zee et al. [15] were able to increase the rate of remission from 51% with radiation therapy alone to 73% with the addition of hyperthermia ($p = 0.01$). They treated only locally advanced, muscle-invasive urinary bladder cancer [15].

Soft tissue sarcoma

As it stands, the LBI Report does not consider the results of the EORTC-ESHO Intergroup Study, as published by the German Soft Tissue Sarcoma Study Group [22], since the original article was published in May 2010.

With 342 patients evaluated, this was the largest randomized Phase III trial [22] for soft tissue sarcomas in adult patients with an elevated risk of recurrence and metastasis. The study demonstrated a statistically significant benefit in local progression-free and disease-free survival (DFS), for the addition of regional hyperthermia (RHT) to chemotherapy, as compared to use of chemotherapy (etoposide, ifosfamide, Adriamycin) alone. The addition of RHT to chemotherapy also reduced the frequency of tumor progression by a third, when compared to the chemotherapy alone control group. An analysis of patient data shows a significant benefit in the rate of overall survival from the addition of hyperthermia for the 267 patients who received full induction therapy in both study groups and the prescribed eight RHT therapy sessions in the experimental group.

As of January 2012, these study results have been adopted by UpToDate and (recently) by the NCCN Guidelines (Version 2/2011), thus, clearly signaling the value of RHT for this disease entity [23]. For this achievement, the Study Group received the 2011 Clinical Science Prize from the Medical Oncology Working Group ("Arbeitsgemeinschaft für Internistische Onkologie", AIO) of the German Cancer Society. That these results—which received a high-profile presentation as early as 2007 at the Annual Meeting of the American Society of Clinical Oncology (ASCO 2007)—did not find their way into the Final Report of the LBI Ludwig Boltzmann Institute is a glaring omission and needs to be explained [24].

Technical developments and quality management

The LBI report makes no attempt whatsoever to consider the quality of hyperthermia treatments and, as one example, accepts at face value the publication of the Indian cervical cancer study (Vasanthan et al., 2005 [13]) as firm proof that hyperthermia combined with radiotherapy is an ineffective form of treatment. Yet the Indian cervical cancer study was harshly criticized for the lack of even basic quality control, since the patients in the study received hyperthermia treatment that was qualitatively inadequate (see "Cervical cancer" section above). In the interim, the Study Group for Clinical Hyperthermia Research (Atzelsberg Circle) has drawn up quality criteria for the clinical application of hyperthermia. These are binding for the member countries of Germany, the Netherlands, Austria, and Switzerland and have been published as a Guideline in a high-ranking source [25]. These criteria are intended to ensure that a high quality, readily identifiable, and comparable hyperthermia procedure is delivered and that the delivered hyperthermia treatments permit valid scientific evaluation.

Conclusion

In summary, we completely reject the main conclusion of the LBI Report. In its place, we draw on the sum total of available literature to conclude that there is ample evidence to state that hyperthermia improves not only local control but also disease-free survival—and in subgroups even overall survival—for the cancers discussed in this paper, when applied in combination with radiation therapy or chemotherapy (e.g., as in the case of soft tissue sarcomas). In this context, we also make reference to the successful studies using local hyperthermia for inoperable melanomas and inoperable recurrence of head and neck cancers [26, 27].

Key deficiencies in the report are as follows:

The period considered. The LBI Report cites as authoritative statements made in the 2004 Report from the German Joint Federal Committee (JFC) and, thereafter, considers only such relevant scientific publications from 2005 and 2009 as accessible through PubMed. Supplementary to the list given in our rejoinder, we must also mention the positive 2010 study from Huilgol et al. [28] on the application of hyperthermia for recurrent head and neck cancers. Regrettably, this study was published after the period of time considered by the LBI dossier. This 2010 study is nonetheless important in buttressing the evidence for the hyperthermia model and the numerous preceding Phase II and Phase III trials for head and neck cancers, such as those published before 2005 [29], which are capable of influencing the ultimate conclusions drawn concerning hyperthermia.

Since only a comparatively small number of institutions apply hyperthermia correctly for appropriate indicators and in a quality-controlled manner—and since one cannot expect an adequate number of positive clinical trials to be generated in a 5-year period—conclusions concerning the clinical value of hyperthermia should take into account the

sum total of studies conducted over the last 20 years [26].

Literature omitted. The Report considers no data that is not part of the JFC Report, although such data would have been available at the point in time in question. The first example is the EORTC 62961-ESHO Phase III intergroup trial initiated by the German Soft Tissue Sarcoma Study Group, which evaluated the value of hyperthermia in treating soft tissue sarcomas. While first published in 2010, summaries of this key study—which also produced positive results for regional hyperthermia—were nonetheless available from 2007 onwards [24]. Furthermore, the Cochrane analysis of Lutgens et al. [14] on cervical cancer (see above) was also ignored. This paper utilizes meta-analysis to show a significant positive effect for hyperthermia treatment, when applied in combination with radiation therapy, both on local control and survival. Nor does the report mention the publication of the positive Phase III trial from 2003 by Colombo et al. [21] on the effects of hyperthermia for superficial bladder tumors. The positive results of this study have since been confirmed in multiple later Phase II bladder cancer trials—although none of these trials are mentioned in the Report either [18, 19, 20].

Misinterpretation of data. While the LBI authors criticize the low numbers of trial patients in the respective hyperthermia studies, they clearly fail to acknowledge that these low numbers are adequate if one considers the very high positive effect achieved by additional hyperthermia (improved local control and survival of around 20%). Furthermore, if one considers these undisputed positive results, further studies on the value of hyperthermia in combination with radiotherapy for cervical cancer and chest wall recurrence are simply ethically unconceivable and will, therefore, not be carried out within western Europe for these same exact reasons.

A further misinterpretation is to allege that a survival benefit is lacking in hyperthermia studies on chest wall recurrence and melanomas. From the outset, these studies were never designed to prove a survival benefit. The primary endpoint in each case was local tumor control—an area where complementary hyperthermia achieved significant improvements [3, 9, 10, 12]. In any case, a survival benefit for a patient group with a recurrent or metastasizing disease is generally not to be expected. On the other hand, improved local control achieves a better quality of life and is, thus, a relevant medical goal. Many other oncological treatment options whose primary objective is palliative care or local tumor control are generally accepted as being part of standard therapy.

Finally, a formal objection. The Report issued by the German Joint Federal Committee (JFC Report) explicitly states that the sole purpose of its research concerns the investigation of the clinical value of hyperthermia in outpatient care and concludes that the costs of hyperthermia treatments in an outpatient context should not be borne by insurers. The JFC Report also concludes that clinical hyperthermia should be investigated further in the hospital setting [1].

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