Hyperthermia a Treatment for Cancer: Maturation of its Clinical Application

G. C. van Rhoon, J. van der Zee

Erasmus MC, Department of Radiation Oncology, Hyperthermia unit, Rotterdam, The Netherlands

Abstract

Hyperthermia (HT) is considered a valuable anti-cancer treatment modality in many Western countries. For advanced cervical cancer adding HT to radiotherapy (RT) doubles the 3 years survival rate (27 vs. 51%). For recurrent breast cancer in earlier irradiated areas the local control rate for RT+HT is doubled compared to RT alone (39 vs. 79%). The doubling of local control – or survival rate following the addition of HT to conventional therapies without increased toxicity is, in historical perspective, an extraordinary and unsurpassed finding. Generally, HT is applied by electromagnetic radiation and requires the use of complex high technological equipment. A strong relation exists between treatment quality and clinical outcome; hence controlled delivery of heat is the Achilles heel of the treatment.

Keywords: Hyperthermia, electromagnetic heating, dosimetry, quality assurance, clinical response

Clinical trials demonstrating the potential of hyperthermia in cancer treatment (Table 1).

Hyperthermia (40-45 °C for 15-60 min.) is always implemented as part of a multimodal, oncology strategy, i.e. in combination with radiotherapy (RT) or chemotherapy (ChT). Extensive biologic research has shown that hyperthermia (HT) is one of the most if not the most potent modifier of RT known today [1]. A recent review [2] on state of the art HT describes selected phase I or II (n=17) and phase III trials (n=16) investigating the effect of HT combined with RT (n=10 trials), ChT (n=15 trials), or both (n=8 trials) in a total of more than 2200 patients. Table 1 shows the results of all phase III trials conducted by Western research group. All studies but two show a statistical significant higher (up to a doubling) tumor control and/or cure rate for the combined treatment modality. Additionally all studies report comparable acute and late toxicity in both treatment arms. The positive results of the most recent trials explain the renewed enthusiasm in hyperthermia, which is reflected in the growing number of institutes interested in the application of hyperthermia [3,4].

Impact of the quality of the hyperthermia treatment on clinical outcome

The importance of adequate heating in HT is well illustrated by the two studies, which failed to show a statistical significant benefit for the HT group. In the trial published by Emami et al. [8] only one patient out of 86 fulfilled the minimal adequacy criteria for the delivery of the HT treatment. In the RTOG [12,13] study patients with small chest wall tumors (≤3 cm) in the study arm (i.e. with HT) responded better in comparison to the control arm, but this was not the case for patients with large chest wall tumors. The phase III trials coordinated by Vernon et al. [7] and Overgaard et al. [9] demonstrated a statistical significant therapeutic advantage of the addition of HT. However, also in these studies the authors reported that the benefit of HT for the larger tumors is less obvious in the case of primary inoperable breast cancer [7] and for melanoma lesions with a diameter >4 cm [9]. In accordance with the RTOG studies these authors report that the poorer outcome for large tumors may reflect the lower ability to heat them adequately. Overall the positive phase III trials demonstrate that HT applied with the current state of the art technology,
possesses a great promise to improve clinical outcome for advance cancers. Nevertheless, there exists a strong need to further improve the HT technology by developing site-specific HT systems and more sophisticated methods to assess the quality of the treatment.

### Maturation of hyperthermia technology

Heating tissue for hyperthermia involves complex technology, physiology and biology. The majority of the hyperthermia treatments are applied using external devices, employing energy transfer to the tissue by RF or MW technology and to a lesser extend ultrasound technology [14].

Since the early seventies, research has been directed at the development of techniques to apply and control hyperthermia. Therapeutic temperatures could be achieved in deep-seated tumors using the first generation equipment for deep loco-regional HT, but it appeared to be difficult to fulfill the temperature-time goals. To overcome these problems the second generation of the radiative deep heating devices, such as the BSD2000 system [15], the four-wave-guide system [16], and the coaxial TEM applicator [17] provided the possibility of SAR-steering by phase and amplitude control or by re-positioning the patient. The third generation equipment is characterized by an accurate control of phase and amplitude steering (e.g. solid state amplifiers with integrated phase-locked loop systems) and use of a more complicated applicator design, e.g. the Sigma Eye with 24 instead of the Sigma 60 with 8 dipole elements. At present, the BSD2000 with the Sigma-60 or Sigma Eye applicator is the most common deep HT-system in clinical use. Clinical experience with the BSD2000 indicates that indeed higher temperatures for longer periods, i.e., a better quality of the HT treatment, can be achieved.

Facilitated by the enormous progress in computational power, the last decade has brought significant advances in Hyperthermia Treatment Planning Systems (HTPS). The currently most advanced 3-d models, having dynamic non-uniform grid generation and conformal 3D FDTD scheme supporting high resolution models at critical structures, are expected to allow a priori selection of the optimal energy deposition or temperature distribution.

The introduction of Non Invasive Thermometry (NIT) by Magnetic Resonance Imaging (MRI) represents the last major technological improvement. Since the clinical introduction of hybrid hyperthermia systems [18-21] it is possible to perform on-line NIT during high power RF-heating. The important potential benefits of NIT can only be valued properly if placed against the limitations of the only other option to assess some form of a quality indicator of the heat treatment, i.e. through invasive thermometry. The temperature-meters used for invasive thermometry are characterized by high accuracy, high temporal and spatial resolution. However, in order to obtain high quality thermometry the temperature probes must be placed at the critical locations [22-24]. In practice, however, the number of interstitially (or intra-luminal) placed temperature probes are limited and reserved to “reachable” locations and thus invasive thermometry provides in nearly all cases only accidental temperature information which is at best more or less representative for the overall temperature distribution.

The results obtained thus far with NIT by MRI-technology are very promising and demonstrate its feasibility. Although, the temperature distribution is still characterized by a relatively low accuracy and low temporal

### Table 1. Comparison of the results of radiotherapy (RT) versus radiotherapy plus hyperthermia (RT + HT) in randomized trials from Western research groups.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumor</th>
<th>Endpoint</th>
<th>N</th>
<th>RT</th>
<th>RT + HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. [26]</td>
<td>Various superficial</td>
<td>Complete response rate</td>
<td>109</td>
<td>42%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>All tumors</td>
<td></td>
<td>39</td>
<td>24%</td>
<td>68%</td>
</tr>
<tr>
<td>Van der Zee et al. [5]</td>
<td>All Pelvic tumors*</td>
<td>3 years overall survival</td>
<td>358</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td></td>
<td>143</td>
<td>22%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td></td>
<td>101</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Cervix*</td>
<td></td>
<td>114</td>
<td>27%</td>
<td>51%</td>
</tr>
<tr>
<td>Sneed et al. [6]</td>
<td>Glioblastoma multiforme*</td>
<td>2 years survival</td>
<td>112</td>
<td>15%</td>
<td>31%</td>
</tr>
<tr>
<td>Vernon et al. [7]</td>
<td>Breast cancer*</td>
<td>complete response rate</td>
<td>308</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Emami et al. [8]</td>
<td>Various</td>
<td>2 years survival</td>
<td>184</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>Overgaard et al. [9]</td>
<td>Melanoma*</td>
<td>2 years local NED</td>
<td>134</td>
<td>28%</td>
<td>48%</td>
</tr>
<tr>
<td>Valdagni et al. [10,11]</td>
<td>Head &amp; neck*</td>
<td>complete response rate</td>
<td>44</td>
<td>41%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>5 years survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez et al. [12,13]</td>
<td>Various</td>
<td>complete response rate overall</td>
<td>236</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>in small tumors (diam. &lt;3 cm)</td>
<td></td>
<td>55</td>
<td>39%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>in large tumors (diam. &gt;3 cm)</td>
<td></td>
<td>181</td>
<td>27%</td>
<td>25%</td>
</tr>
</tbody>
</table>

N= number of patients; NED = no evidence of disease; * Statistical significant difference.
resolution, a most important progress is achieved as NIT by MRI provides complete 3-dimensional temperature information. The availability of 3D temperature information is crucial to optimize the energy distribution in the target region as well as to reduce the effect of unwanted hot-spots elsewhere in the body during regional hyperthermia treatments. The logical next step to refine the application of HT will be on-line control of the transferred power deposition pattern in order to re-adjust the heating system to achieve an improved temperature distribution as illustrated in figure 1.

Finally, MR monitoring during HT is also a mandatory tool to derive spatial information on the physiological (perfusion, flow, oxygenation) processes that are temperature dependent and their change may play a significant role as prognostic factor for the outcome of the multimodality treatment for cancer [25,26].

**New knowledge in prognostic factors for hyperthermia**

Since the 1980s thermal cytotoxicity has been the foundation for the HT treatment design with a temperature goal for a $T_{90}$ of 43 °C during 60-90 minutes for 4-8 sessions. Under pressure of the good clinical results of the phase III trials despite the reported low $T_{90}$'s (39-41 °C) in all studies, the appropriateness of this view is now strongly questioned.

The positive results obtained in many phase III trials at temperatures too low for significant cytotoxicity, cause abandoning of the “conventional view”, and boosts international and multi-disciplinary discussions towards better understanding of the biological processes involved in HT at realistic, i.e. clinically achievable temperatures [27]. Current new biology concepts for dosimetry in HT are considering all effects occurring in the temperature range of 39 to 44 °C that is commonly achieved during clinical treatments. The special issue of the Int J Hyperthermia of December 2005 “Thermal Medicine, Heat Shock Proteins and Cancer” presents an excellent overview of the wide range of biologic effects involved in HT: inhibition of radiation-induced damage repair, changes in perfusion, re-oxygenation, induction of heat shock response and immunological stimulation, etc. Needless to say is that the interactions between the mechanisms and their temperature-time dependency adds an additional degree of complexity. Hence, exploitation of these compelling mechanisms in a treatment strategy and capturing the effectiveness of the HT treatment in a single “dose”-parameter will be a particular demanding challenge.

**Fig. 1.** Schematic lay-out of the treatment optimization protocol for loco-regional hyperthermia in a hybrid system as proposed by P. Wust, Charité Medical Center, Berlin.
References


