

# The role of hyperthermia in the battle against cancer

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## ABSTRACT

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**Aims and background.** Hyperthermia, the heating of tumors to 41.5-43 °C, could be today considered the fourth pillar of the treatment of cancer. Employed for 20 years in Europe, the USA and Asia, hyperthermia, used in addition to radiotherapy, chemotherapy and surgery, increases both local control and overall survival, restores the chance of the surgery for inoperable tumors and allows a new low-dosage treatment of relapsed cancers previously treated with high radiotherapy dosage without increasing toxicity.

**Methods.** Hyperthermia can be either superficial, produced by a microwave generator, or regional, produced by a radiofrequency applicator with multiple antennas, which emanate a deep focalized or interstitial heating.

**Results.** The results are confirmed by phase III randomized trials, with level 1 evidence. A review of the international literature on hyperthermia, the experience of the University Hospital of Verona Radiotherapy Department (Italy) and a summary of the Symposium regarding the Evolution of Clinical Hyperthermia plus Radiotherapy during the Twentieth Congress of the French Society of Radiation Oncology (SFRO) are presented.

**Conclusions.** Hyperthermia is an important treatment modality in cancer treatment and its results are strongly supported by criteria of evidence-based medicine. Fifteen years of experience of the Radiation Oncology Department in Verona confirms the positive results obtained with international prospective trials, with level 1 evidence. Hyperthermia appears to be the fourth pillar beside surgery, radiotherapy and chemotherapy. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

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## Introduction: Thermobiology

Hyperthermia is the elevation of temperature inside a tumor, up to 41.5-43 °C, without exceeding the limits of tolerance of neighboring normal tissues. In fact, temperatures more than 45 °C are used for thermal ablation. Hyperthermia can be either superficial, produced by a microwave generator, or regional, produced by a radiofrequency applicator with multiple antennas, which emanate a deep focalized heating, saving the skin, or interstitial heating. In all these systems the radiations are non-ionizing, in which the energy presents a heterogeneous distribution inside the tissues, depending on their thermal characteristics and on blood perfusion.

The main actions of hyperthermia in the neoplastic tissues are the following:

- greater heat sensitivity of neoplastic tissues to hyperthermia, due to its chronic ischemia, hypoxia and acid pH;
- lethal effect of temperature of 42-43 °C on tumor cells, depending on the application time;
- temporary growth stabilization of tumor cells after a moderate hyperthermia (39-41 °C);
- prolonged action of temperature, due to lower thermal dissipation, caused by a chronic ischemia inside the tumor, as a result of its reduced vessel regulation mechanisms;

**Key words:** chemotherapy, hyperthermia, level 1 evidence, radiotherapy.

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- alterations in the neoplastic cell cycle, which lead to the blocking of mitosis, due to a disruption in the S phase;
- marked action on the core of the tumor, less sensitive to radiation because of ischemia, hypoxia and low pH;
- action in favor of apoptosis mechanisms.

### **Rationale for radiotherapy + hyperthermia association**

1) Hyperthermia increases perfusion and oxygenation of neoplastic hypoxic cells, which are three times more resistant to ionizing radiation than normal cells. Consequently, the action of radiotherapy becomes 1.5-5 times more efficient. Hyperthermia has a direct cytotoxic action on cancer: due to the pathologic blood vessels, the thermal elevation persists inside the tumor, whereas neighboring normal tissues, adequately perfused, are cooled: at 43 °C, normal cells are not damaged, whereas tumor cells are damaged at the cell nucleus, plasmatic membrane and cytoskeleton, up to apoptosis. Hyperthermia acts mostly at an acid pH and in the S phase of the cell cycle, when cells are radioresistant. This means that radiotherapy and hyperthermia are complementary in their action: radiotherapy forms free radicals, which damage the DNA of tumor cells, whereas hyperthermia inhibits its repairation.

2) Hyperthermic inhibition of repairing radiation damage has been suggested as an essential factor causing the synergistic cell-killing effect of X-rays and hyperthermia. Heating cells before X-irradiation has been shown to inhibit the repair of DNA strand breaks as well as the excision of base damage<sup>1</sup>. There are several DNA repair pathways involved in restoration of damage after ionizing irradiation and the kinetics of all of them are affected by heat shock. However, this does not imply that the inhibition of each of these pathways is relevant to the effect of heat on cellular radiosensitivity. Data reported by Kampinga *et al.*<sup>2</sup> in 2004 showed that thermal inhibition of the non-homologous end-joining pathway plays a role in heat radiosensitization. Furthermore, limited data suggest that the homologous recombination pathway may not be a major heat target. The inhibition of base-excision damage repair could be, by deduction, the crucial step in the mechanism of radiosensitization by heat<sup>2</sup>.

3) Hyperthermia enhances the sensitivity of cells to radiation and drugs and this sensitization is not directly related to altered heat-shock proteins (HSP) expression. Elevating HSP prior to heating makes cells thermo-tolerant and altering their expression will affect the extent of thermal action because the HSP will attenuate the heat-induced protein damage, responsible for radiation and drug sensitization. Nuclear protein damage is considered to be responsible for hyperthermic effects on DNA repair, especially base-excision damage repair<sup>3</sup> (Figure 1).

### **Rationale for chemotherapy + hyperthermia association**

Hyperthermic drug sensitization can be seen for several anti-cancer drugs, in particular alkylating agents. The combined action between heat and drugs arises from multiple events such as drug accumulation, drug detoxification pathways and repair of drug-induced DNA adducts. Cells with acquired drug resistance can be made responsive to the same drugs again by combining drugs with heat.

Hyperthermia, which increases tumor tissue perfusion, facilitates the absorption of chemotherapeutic drugs through cell membrane. The heat accelerates chemical reactions, so that chemotherapy becomes more effective, without being more toxic. Hyperthermia allows the response of tumors resistant to various chemotherapeutic drugs: doxorubicin, cisplatin, bleomycin, mitomycin c, nitrosoureas, cyclophosphamide. Use of liposomes, including adriamycin (Caelyx®) administered i.v., hyperthermia fuses and frees their content inside the heated tumor bed, thus obtaining a target chemotherapy, with reduction of side effects.

On March 18, 2010, the Celsion Corporation (<http://www.celsion.com>, accessed 17 November 2010) announced that an abstract about the phase I/II trial of ThermoDox® in recurrent chest wall cancer has been accepted for presentation at the American Society of Clinical Oncology (ASCO) 2010 Annual Meeting. The abstract presents the background, rationale and design of the DIGNITY study which is ongoing and evaluating ThermoDox® in combination with hyperthermia in women with recurrent breast cancer on their chest wall<sup>4</sup>. In a separate trial with a similar design being conducted at Duke University Medical Center, researchers are reporting convincing evidence of clinical activity. The DIGNITY clinical trial is a phase I/II, open label, dose-escalating trial to evaluate the safety and efficacy of ThermoDox® with hyperthermia for the treatment of recurrent chest wall breast cancer, an aggressive form of cancer with a poor prognosis and limited treatment options. The primary end point in the DIGNITY trial is durable complete local response at the tumor site. Once the safe dose is determined, Celsion intends to enroll up to 100 patients to establish efficacy. The results from the DIGNITY trial are expected to build on the promising data from the phase I dose-escalation study currently being conducted at Duke University Medical Center. ThermoDox® has also demonstrated evidence of efficacy in a phase I study for primary liver cancer. Celsion has been granted FDA orphan drug designation for ThermoDox® and is conducting a pivotal 600 patient global phase III study in primary liver cancer under an FDA special protocol assessment, thus obtaining a target chemotherapy, with reduction of side effects.

## Research studies

It has been demonstrated that hyperthermia also has an anti-angiogenic action and an immunotherapeutic role, due to thermal shock proteins, which are produced by stressed tumor cells. Finally, hyperthermia sustains the action of genic therapy<sup>5-9</sup>.

The immunotherapeutic role of hyperthermia is not yet completely understood. Especially, the effects on natural killer (NK) cell cytotoxicity against tumor cell targets have not been fully demonstrated. At treatment temperatures above 40 °C, both enhancing and inhibitory effects of cytotoxic activity of NK cells against tumor cells have been reported. In particular, an enhancement of human NK cytotoxicity against tumor cell targets has been demonstrated using a temperature of 39.5 °C<sup>10</sup>.

Data in the literature indicate a strong potential for heat-induced enhancement of NK cell activity in mediating the improved clinical response. A better understanding in this field should be achieved in order to maximize the clinical benefits obtained by using hyperthermia for cancer therapy.

## Main international results of clinical applications of hyperthermia

There are three criteria for a correct utilization of hyperthermia: 1) it must be necessary, e.g., to improve unsatisfactory clinical results; 2) its efficacy must be demonstrated by experimental and clinical studies; 3) the results must show a favorable relationship between costs and efficiency.

### *Clinical studies with exclusive hyperthermia*

Fourteen studies from 1979 to 1990, including 343 patients, showed a complete remission (CR) in 13% of cases, (0-40%), a CR plus a partial remission (PR) in 51% of cases<sup>11</sup>. In general, only superficial and small tumors could be heated by a valid temperature inside the treated volume; the median duration of response was limited to 6 weeks. Three additional studies reported complete response rates of 11%, 16% and 18%. Only small and superficially located tumors can be heated to an adequate level over the whole volume, and the response duration is short (median, 6 weeks). Relatively strong evidence comes from several studies on "matched lesions": multiple lesions within the same patient were treated with radiotherapy alone or with irradiation combined with hyperthermia. The total 713 lesions examined showed an increase in CR rate from 31% to 67% by adding hyperthermia<sup>12-14</sup>.

In 1989, the Consensus Conference held in Trento (Castel Ivano) on hyperthermia concluded that the exclusive use of hyperthermia cannot be recommended<sup>15</sup>.

### *Clinical studies with radiotherapy + hyperthermia association*

From 1989 to 1998, clinical data allowed to obtain some levels of evidence sufficient to establish some recommendations for the use of hyperthermia<sup>16-20</sup>. In 2004, a clinical group consensus was founded in Osaka (Kadota Fund International Forum, Kadota, Japan), and its conclusions were published in 2008<sup>21</sup>. A first review was published in 1989 by Overgaard, who evaluated the results of nonrandomized studies of 24 authors from the USA and Europe in 2,234 patients affected by a head and neck tumor, breast cancer, or melanoma<sup>22</sup>. The paper demonstrated that the 36% CR rate obtained with exclusive radiotherapy (0-50%) was almost doubled with radiotherapy + hyperthermia (69.5%; 7-100%).

Some multicentric studies on a large scale, with level 1 evidence, showed that hyperthermia combined with radiotherapy comparing with radiotherapy alone improves the results *versus* hyperthermia alone in the following tumors: head and neck, melanoma, breast, esophagus, soft tissues sarcomas, pelvic tumors (bladder, rectum, uterine cervix), glioblastoma multiforme, and superficial tumors (Tables 1 and 2).

### *Head and neck tumors*

In 1994, an Italian phase III study, conducted by Valdagni and Amichetti<sup>23</sup> on 41 patients affected by stage IV inoperable head and neck cancer, showed that the association radiotherapy + hyperthermia increased the CR rate from 41% to 83%, 5-year local control rate from 24% to 68%, and 5-year overall survival from 0% to 53%, *versus* radiotherapy alone.

### *Melanoma*

In 1996, a Danish phase III study published by Overgaard *et al.*<sup>24</sup> and including 70 patients with relapsed or metastatic melanoma, obtained these results: CR, 35% with radiotherapy, 62% with radiotherapy + hyperthermia; 5-year disease-free survival (DFS), 28% with radiotherapy, 46% with radiotherapy + hyperthermia.

### *Breast cancer*

In the same year, an English phase III study, coordinated by Vernon *et al.*<sup>25</sup> and including five randomized studies and 306 patients affected by a localized tumor, obtained in the group treated with radiotherapy + superficial hyperthermia an increase in CR rate from 41% to 59% and in DFS from 30% to 50%, *versus* the group treated with radiotherapy alone.

### *Esophageal cancer*

In 1996, a Chinese study published by Wang *et al.*<sup>26</sup> on 125 patients affected by an esophageal cancer, treated with radiotherapy + chemotherapy with or without regional hyperthermia, reported an almost twofold in-

**Table 1 - Randomized studies examining the effects of superficial hyperthermia combined with radiotherapy on response and survival**

AA	Site	Control arm	Experim arm	N° pts	Endpoint	Ht better	Survival benefit
Perez 1991	H&N + breast	RT	RT + HT	245	Response	Possibly	No
Overgaard 1995	Melanoma	RT	RT + HT	68	Response 62% vs 35%	Yes	Yes
Valdagni 1993	H°N (N3)	RT	RT + HT	44	Response 83% vs 41%	Yes	Yes 5-yr survival 53% vs 0%
Vernon 1996	Breast (advanced or recurr)	RT	RT + HT	307	Response 59% vs 41%	Yes	No
Emami 1992	H&N + breast	RT	RT + HT	173	Response	No	No

H&N, head and neck lymph node; RT, radiotherapy; HT, hyperthermia, AA, Authors.

**Table 2 - Randomized studies examining the effects of regional hyperthermia combined with radiotherapy on response and survival**

AA	Site	Control arm	Experim arm	N° pts	Endpoint	Ht better	Survival benefit
Harima 2001	Cervix cancer (stage III)	RT	RT + HT	40	CR 85% vs 50%	Yes	No
Van der Zee 2000	Pelvic cancer	RT	RT + HT	361	CR 55% vs 39%	Yes	Yes
Issels 2008	Soft-tissue sarcoma	chemo	chemo + HT	>150	DFS	Yes	Yes
Datta 1987	Cervix cancer	RT	RT + HT	64	CR 55% vs 31%	Yes	No
You 1993	Rectal cancer	RT	RT + HT	122	CR 23% vs 5%	Yes	No

H&N, head and neck lymph node; RT, radiotherapy; HT, hyperthermia, chemo, chemotherapy; CR, complete response; DFS, disease-free survival; AA, Authors.

crease in 3-year OS (24% without hyperthermia, 42% with hyperthermia).

#### *Soft tissues sarcomas*

A German phase III study was presented by Issels *et al.*<sup>27</sup> at the ASCO annual meeting of 2007 and included 342 patients affected by a high-risk sarcoma, treated with neoadjuvant chemotherapy + radiotherapy with or without hyperthermia: 37% of the patients treated with hyperthermia obtained a 50% reduction in tumor volume compared to 12% in the group treated without hyperthermia. Median DFS with or without hyperthermia was 30 and 16 months, respectively<sup>27</sup>. The study confirmed a previous American phase III study by Prosnitz *et al.*<sup>28</sup> which obtained 95% local control with neoadjuvant radiotherapy + regional hyperthermia in 97 patients affected by high-risk limb sarcoma.

#### *Locally advanced pelvic tumors*

A Dutch multicentric trial, conducted by van der Zee *et al.*<sup>29</sup> on 358 patients, concluded that regional hyperthermia added to radiotherapy increased the CR rate from 51% to 73% in bladder tumors and from 57% to 83% in uterine cervix cancer compared to radiotherapy alone.

Overall survival increased from 27% to 51%. As regards advanced rectal cancer, in 1993 a Russian study published by Berdov and Menteshashvili<sup>30</sup>, who added regional hyperthermia to radiotherapy, reported an increase in 5-year overall survival from 7% to 36% *versus* radiotherapy alone.

A recent Cochrane review<sup>31</sup> concluded: "Taken the limited number of patients available for this analysis, the over-representation of FIGO stage IIIB disease and the methodological flaws as discussed, it is not possible to draw definite conclusions regarding the beneficial effect of hyperthermia added to standard radiotherapy. Treatment-related severe toxicity, i.e. grade 3 to 4, seems not to be affected by the addition of hyperthermia to standard radiotherapy treatment. However, the available data do suggest that superior local tumor control rates and overall survival can be achieved in patients with locally advanced cervical cancer by adding hyperthermia to standard radiotherapy. Although the available data mainly apply for patients presenting with FIGO stage IIIB disease, radiobiological considerations suggest a possible benefit for its use in other locally advanced stages as well".

Regarding advanced rectal cancer, results are more controversial. A recent Cochrane review<sup>32</sup> concluded that: "To make a firm conclusion further studies are

needed to compare chemo-radiation versus thermo-radiation versus chemo-radiation plus hyperthermia in well-selected and quality controlled randomized trials. We concluded that the given hyperthermia varied widely, which makes comparison of the results very difficult. Also, it should be stated that upfront selection of patients with locally advanced cancer by new techniques (MRI, CT scanning of the abdomen) is mandatory.”

#### *Glioblastoma multiforme*

In 1998, an American phase III trial, published by Sneed *et al.*<sup>33</sup> on 112 patients, showed that the 2-year overall survival rate was doubled in patients treated with brachytherapy + interstitial hyperthermia *versus* patients treated without hyperthermia.

#### *Superficial tumors*

In 2001, a phase III randomized trial published by Jones *et al.*<sup>34</sup> on 109 patients affected by chest wall metastases from breast cancer, melanoma, or a relapsed head and neck tumor obtained a CR of 66% in patients treated with radiotherapy + hyperthermia and of 42% in those treated without hyperthermia. The results were even more impressive in patients previously treated with radiotherapy in the past, with a CR of 68% with and of 24% without hyperthermia.

According to the recommendations of the European Society for Hyperthermic Oncology (ESHO), a number of tumor types are treatable with hyperthermia: carcinomas of the bronchus, ovary, colon, pancreas and liver, Hodgkin's disease, non-Hodgkin lymphoma, mesothelioma, germ cell tumor. For the last two types, the therapeutic benefit of adding regional hyperthermia to radiotherapy and chemotherapy are proved by level 2 evidence studies<sup>21</sup>.

#### *Retreatment of already irradiated tumors with radiotherapy + hyperthermia*

In 1998, van der Zee *et al.*<sup>35</sup> published a study conducted on 97 patients affected by a breast cancer relapse in an already treated zone, using a radiotherapy dose of 4 Gy per fraction, twice weekly for 4 weeks, i.e., 32 Gy in 8 fractions, plus 1 hyperthermia session every radiotherapy day. The results of this protocol, well tolerated, were the following: a median response of 4 months for PR and of 26 months for CR. The median overall survival for all patients was 12 months.

### **Experience of hyperthermia at the Radiation Oncology Department in Verona (Italy)**

The Radiation Oncology Department of the Azienda Ospedaliera Universitaria Integrata in Verona (Italy), where in 2001 and June 2009 whereas held the 19th and 25th Annual Congress of the ESHO, could be considered

the national referring center of hyperthermia for Italy. Our new machines, a BSD Sigma Eye system (BSD Medical Corp., Salt Lake City, Utah, USA) with a radiofrequency antenna arrays for 3D regional hyperthermia (Figure 2) and a BSD 500 system employing a microwaves generator for superficial hyperthermia, obtain a precise and noninvasive thermometry. The hyperthermia session, which lasts about 1 hour, begins a short interval after the radiotherapy session; it is performed once weekly for regional hyperthermia and once or twice weekly for superficial hyperthermia, in order to avoid a thermal resistance, induced by HSP. Before the start of treatment, a provisional thermal map is achieved by using the HyperPlan system (Figure 3).

#### *HyperPlan system for regional hyperthermia*

HyperPlan is a software system for performing 3D simulations and treatment planning in regional hyperthermia. It allows the user to understand the complex effects of electromagnetic wave propagation and heat transport inside a patient's body. Optimized power amplitudes and phase settings can be calculated for the BSD radiowave applicators Sigma-60 and Sigma-Eye. The planning system as well as the underlying numerical algorithms have been developed at the Zuse Institute Berlin in cooperation with the Charite Berlin, Campus Virchow-Klinikum. The work has been supported by Dr. Sennewald, Medizintechnik GmbH, Munich.

HyperPlan is built on top of the modular, object-oriented visualization system “AMIRA”. The system already contains powerful algorithms for image processing, geometric modeling and 3D graphics display. HyperPlan provides a number of hyperthermia-specific modules, allowing the user to create 3D tetrahedral patient models suitable for treatment planning. In addition, all numerical simulation modules required for hyperthermia simulation are part of HyperPlan.

The addition of hyperthermia to radical, palliative, neoadjuvant or adjuvant radiotherapy, according to the guidelines of the ESHO<sup>11</sup>, is reserved for high-risk cases, since superficial hyperthermia is employed in head and neck pN2 tumors with capsular rupture, when there is an infiltration of soft tissues of the neck, a pTR1–2 tumor, or an N3 inoperable tumor. Other indications are the following: chest wall metastases in breast cancer patients, bulky lymphomas, huge inguinal, axillary or supraclavicular adenopathies, metastases from melanoma, and Kaposi sarcoma.

Regional hyperthermia is employed to treat sarcomas, advanced or relapsed pelvic tumors, retroperitoneal pathological lymph node adenopathies, carcinoma of the pancreas, esophagus, stomach and cardias, peritoneal metastases from ovarian carcinoma, and liver metastases from gastrointestinal tumors.

The so-called “van der Zee” protocol, which uses electrons or photons, allowed us to retreat a number of pa-

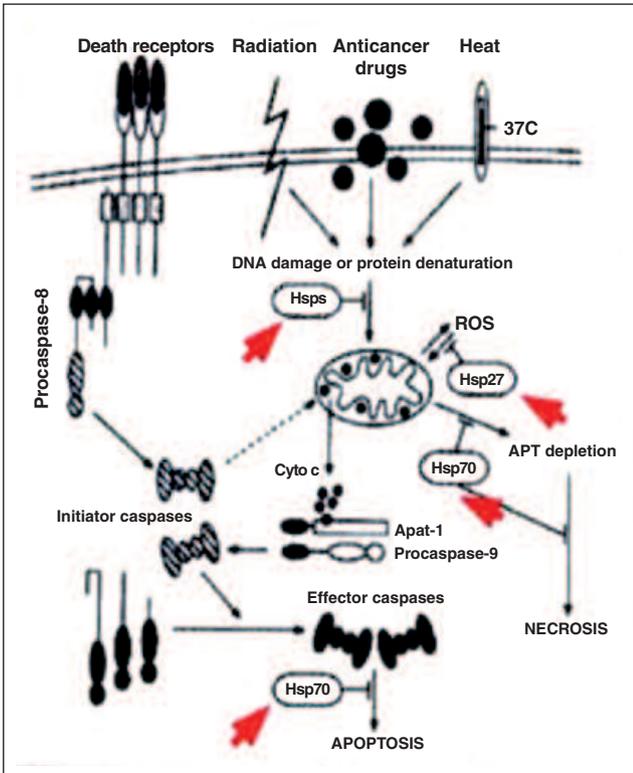


Figure 1 - Heat-shock proteins (HSP) prior to heating makes cells thermo-tolerant.



Figure 3 - Hyperplan system.



Figure 2 - BSD 2000 Sigma Eye 3-D system.

tients who presented a relapse of a superficial or pelvic tumor, in areas already treated with a radical dose of radiotherapy. In these cases, retreatment with a low dose would be ineffective, whereas a high dose would have caused radionecrosis. This protocol, very useful not only for palliation but also in inoperable or metastatic breast cancer, could also obtain a local CR. There are few contraindications for using regional hyperthermia: severe cardiac disease, presence of a pacemaker, and metallic hip prosthesis.

## Results of published studies in our Institution

### *Advanced uterine cervix cancer*

A phase II trial, presented in April 2008 in Munich at the 10<sup>th</sup> Congress of the International Conference of Hyperthermic Oncology, performed on 18 patients treated with radiotherapy + regional hyperthermia + radiosensitizing cisplatin, obtained a CR of 66% and a PR of 34%. At a follow-up of 44 months, DFS was 50% and overall survival was 66%. This trimodal treatment protocol was well tolerated, and its results were very promising<sup>36</sup>.

### *Advanced rectal adenocarcinoma*

A study with a neoadjuvant intensified radiotherapy + chemotherapy + regional hyperthermia in 109 patients affected by T3-4, N0-1, M0 rectal cancer was presented in 2003 at the ASTRO Meeting. The study demonstrated that the addition of regional hyperthermia to 60-64 Gy radiotherapy is able to increase the CR and PR rate in operated patients. CR was also increased in 6 patients who refused surgery, with a 10 year follow-up<sup>37</sup>. A later study in another group of 76 patients obtained a pathologic CR of 23.6%, a pathologic PR of 44.7%, and a no change in 26.3% of patients, with an acceptable toxicity<sup>38</sup>. The authors concluded that preoperative chemoradiation combined with regional hyperthermia resulted in low acute and late toxicity and a good pathologic

CR and conservative surgery rates. Thermal therapy should be considered in forthcoming trials on locally advanced rectal cancer.

#### *Advanced anal canal cancer*

A feasibility study for organ preservation in 13 patients treated with radiotherapy + chemotherapy + regional hyperthermia, presented at the 18<sup>th</sup> National Congress of the AIRO, demonstrated a 5-year DFS of 54% *versus* a 3-year overall survival of 65% obtained in an EORTC trial and a 5-year overall survival of 69% in an RTOG trial. The DFS rate and the good tolerance suggested that we add regional hyperthermia to our protocols of radiotherapy + chemotherapy<sup>39</sup>.

#### *Locally advanced prostate cancer*

In 2007, a prospective phase II trial, performed on 144 high-risk locally advanced prostate cancer patients, employing 3D radiotherapy + regional hyperthermia + androgenic suppression (AS) with LH-RH analogue, with a follow-up of 52 months, obtained a median overall survival of 87.5%<sup>40</sup>. Compared with literature data, the results are satisfactory, considering the stage (T2b-T4 N1) and the irregular administration of AS. In fact, AS was regularly administered for six months following the initial protocol only in 52% of our patients, whereas in other patients AS therapy was in part refused or interrupted. In 2009, a new trial, presented at the 20th National Congress of SFRO, on 20 patients treated with intensity-modulated radiotherapy on the pelvis plus a 3D boost on the prostatic region + regional hyperthermia + AS reported lower toxicity than previously observed in patients treated with irradiation only to the prostate<sup>41</sup>.

#### *Inoperable pancreatic cancer*

From 2000 to 2008, 74 patients affected by locally advanced pancreatic cancer were treated in our department by using chemo-radiotherapy combined or not with regional hyperthermia. Eight patients with distant metastases were excluded and 10 patients were lost to follow-up. Of 56 assessable patients, 30 were treated by using chemo-radiotherapy combined with regional hyperthermia (group 1), whereas in 26 cases, only chemotherapy + radiotherapy was delivered (group 0). In most cases, the chemotherapy consisted of gemcitabine alone. In 9 cases, gemcitabine was combined with 5-fluorouracil or oxaliplatin. Radiotherapy was delivered at a mean dose of 54 Gy (range, 51-56), combined with a regional hyperthermia session once a week in group 1. All patients were affected by a primary tumor, except for 5 patients in group 1 and 7 patients in group 0, who were affected by a local recurrence. At 12 months, 60% of patients in group 1 and 50% in group 0 were alive, with a median survival of 14 *versus* 11 months, with an increase in survival of 3 months in the

group treated by adding regional hyperthermia ( $P = 0.025$ ). This gain increased to 9 months when we considered recurrent and metastatic pancreatic tumors (20 cases), where median survival was 14 months in the regional hyperthermia group and 5 months in the group treated without hyperthermia (mean survival, 21.4 *vs* 10.4 months). Chemotherapy + radiotherapy was well tolerated, without an increase in toxicity in group 1, where regional hyperthermia was added.

The authors concluded that regional hyperthermia, combined with chemotherapy + radiotherapy, is a promising therapeutic modality in the treatment of locally advanced pancreatic cancer, especially in metastatic or recurrent tumors. It does not increase acute or late toxicity of combined treatment. Considering the relatively small number of patients enrolled in the study and the lack of randomization, a new randomized phase III trial is needed in order to evaluate the effectiveness of regional hyperthermia in locally advanced pancreatic cancer<sup>42</sup>.

### **Evolution of clinical hyperthermia during 2009**

On October 23, 2009, during the 20th National Congress of SFRO, a symposium was held on the evolution of clinical hyperthermia in radiation oncology, chaired by Prof. Olivier Le Floch, CHRU in Tours and by Prof. Jacoba van der Zee, from Rotterdam University, with the presence of three other experts: Dr Gérard Devant (BSD Medical Corp., Salt Lake City), Dr Gerard van Rhoon (Rotterdam), and Dr Oliver Ott (Erlangen). Their interventions can be summarized as follows:

- 1) In the hyperthermia field, after 20 years of experience, technological progress is paralleled by that achieved in radiotherapy and nowadays it is guided by imaging. If the state-of-the-art is hybrid regional hyperthermia 3D/MRI systems, installed in Munich and Berlin, the Sigma eye 3D BSD system also obtains a safe and noninvasive thermometry and can produce clear results.
- 2) Quality assurance methods testing hyperthermia, always improved, showed that hyperthermia efficacy is durable. In 2008, a multicentric Dutch trial conducted by Franckena *et al.*<sup>43</sup>, updating the study of van der Zee *et al.*<sup>29</sup>, obtained in 114 females affected by advanced uterine cervical cancer a 12-year DFS of 20% with radiotherapy alone *versus* 37% with radiotherapy + regional hyperthermia. In 2009, another study by the same authors in 378 patients showed similar results<sup>44</sup>. Consequently, the use of radiotherapy + regional hyperthermia can be justified as first-line treatment as an alternative to radiotherapy + chemotherapy.
- 3) Oliver Ott presented the up-to-date results of ESHO studies still ongoing in Erlangen, coordinated by Prof. Sauer, regarding pTR0-1 pancreatic carcinoma, peri-

toneal carcinomatosis, pTR1-2 prostate cancer, rectal cancer recurrences, and anal carcinoma. As regards the latter, the authors pointed out the results of a phase II trial with a 5-year follow-up: in patients without colostomy, overall survival was 68% without regional hyperthermia and 95% with hyperthermia (Personal Communication).

## Conclusions

Hyperthermia, thanks to the improved systems for achieving an optimal distribution of heat inside the tumor and precise and noninvasive thermometry, is today an important treatment modality in the treatment of cancer, and its results are strongly supported by criteria of evidence based medicine. Fifteen years of experience of the Radiation Oncology Department in Verona confirms the positive results obtained with international prospective trials, with level 1 evidence. Hyperthermia is a therapeutic modality that, employing nonionizing radiations, can be used not only by radiation oncologists but also by clinical oncologists. Its addition to radiotherapy with or without chemotherapy is important when it is necessary to treat advanced or high-risk tumors, or to retreat a relapse in a pre-irradiated area. Hyperthermia appears to be the fourth pillar besides surgery, radiotherapy and chemotherapy. Its diffusion is to be hoped for because, against the common enemy, four weapons are better than three.

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