Tumor cells can't stand the heat

*Boosting the effectiveness of hyperthermia in cervical carcinoma*

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Chapter 11

Summary and discussion

Arlene L. Oei
Summary

Cervical cancer is one of the most common and most dreaded cancers in women worldwide. Current therapies show a five-year overall survival of 65% in the treated patients. This indicates, 35% of the patients will die of their disease. Consequently, there is an urgent need to improve current therapies. Hyperthermia has been successfully applied in many different tumor types since the 1980s, and multiple clinical trials have proven that hyperthermia is a successful treatment for patients with locally advanced cervical carcinoma. Radiotherapy is combined with hyperthermia in patients with a contraindication for receiving standard cisplatin-based chemoradiation, e.g. because of kidney failure or neurotoxicity. Although hyperthermia may not be accepted and available for most patients, there is increasing evidence that hyperthermia is the best sensitizer of both radiotherapy and chemotherapy thanks to its specific targeting of tumor cells with minimal damage to normal tissue. Until recently, the molecular effects of hyperthermia were poorly understood. Radiobiological research, such as described in the present thesis, provides increasingly more biological arguments why hyperthermia sensitizes radiotherapy and chemotherapy.

In PART I of this thesis, we explored the possible molecular mechanisms explaining the effectiveness of hyperthermia and generated some hypotheses that were experimentally tested. Additionally, the success of combinational therapy with radiotherapy or chemotherapy and hyperthermia for cervical carcinoma were investigated. In PART II the results are described of our studies to improve current clinical hyperthermia strategies, more specifically, studies leading to a better sequence of, and time interval between hyperthermia and radiotherapy. Finally, in PART III, the experimental studies on the potential benefits of the addition of some promising targeted drugs to multimodality strategies including hyperthermia were described.

Mechanisms of hyperthermia

Hyperthermia triggers multiple mechanisms that sensitize tumor cells to current anti-cancer treatments. Sensitization can be explained at different levels. At tissue level, hyperthermia induces local vasodilatation that will increase oxygen supply to the hypoxic tumor area, thereby making tissue more sensitive to radiation. At the molecular level, hyperthermia has been shown to inhibit multiple DNA repair pathways, as described in Chapter 2. Multiple in vitro and in vivo experiments and many different clinical trials demonstrate that hyperthermia works. Only recently, we are starting to understand the molecular mechanisms involved in sensitization by hyperthermia. Hyperthermia can inhibit homologous recombination (HR), one of the major DNA double strand break repair pathways, but hyperthermia can also inhibit other DNA repair routes. The most prominent mechanism depends on the difference in temperature. The knowledge that hyperthermia can inhibit HR and the ongoing discussion
if hyperthermia interferes with non-homologous end joining (NHEJ), was the basis for the experiments described in Chapter 3. In those experiments, HR incompetent cells - incompetent due to deficiencies in BRCA2 - were compared to wild-type cells to evaluate their sensitivity to hyperthermia. We had expected that hyperthermia in BRCA2 wild-type cells would respond like BRCA2 mutated cells, i.e. that hyperthermia would only inhibit HR. However, hyperthermia in BRCA2 wild-type cells did not give a similar cell survival similar as in BRCA2 mutated cells. And after hyperthermia, BRCA2 mutated cells had a lower cell survival than untreated BRCA2 mutated cells, which suggests that hyperthermia may work through more molecular mechanisms than by interference with HR. The results described in Chapter 2 could not explain why hyperthermia is particularly effective in cervical carcinoma. Therefore, the effects of hyperthermia were investigated in several cervical carcinoma HPV-positive and HPV-negative cell lines, wherein hyperthermia temperatures and treatment times were varied. The results of this study are described in Chapter 4. In HPV-positive cervical cancer cells, the recognition of corrupted ‘infected’ DNA by the p53 protein is disabled by the viral protein E6. Hyperthermia was found to temporarily abolish the suppression of p53 by protein-E6, and thereby temporarily restores the normally required function of p53 and p53-dependent apoptosis.

Dose, sequence and time interval between radiotherapy and hyperthermia

Patients with an inoperable cervical carcinoma, and who have a contraindication for cisplatin-based chemotherapy, can still be effectively treated by radiotherapy plus hyperthermia. However, there is no consensus worldwide about the optimal sequence of and time interval between hyperthermia and radiotherapy. In Europe, the patient generally receives radiotherapy first, followed by hyperthermia; in the United States the therapies are generally performed in the reversed order. The rationale to give irradiation first, is to first induce DNA damage with ionizing radiation before interfering with the DNA repair pathways with hyperthermia to get a maximum effect of radiation. The opposite sequence, often applied in the United States, is based on the idea to maximally exploit vasodilatation and tumor re-oxygenation by hyperthermia. This transatlantic controversy which of both approaches yields the best results, requires thorough investigations wherein treatment sequence and time interval are varied. Such studies in multiple cell lines are described in Chapter 5. The results were a tie: different sequences were not associated with significant differences in cell survival, cell cycle and DNA damage. And as expected, a short time interval between the two therapies resulted in killing a higher number of cancer cells. Both findings are expected when the main mechanism of action is interference with a relatively slow DNA repair mechanism. However, the re-oxygenation mechanism cannot be operational in in vitro experiments, so the issue of the dominant clinical mechanism remains as undecided.
Triggered by these laboratory results, it was feared that prolonged time intervals between radiotherapy and hyperthermia could also be detrimental in real patients. Therefore, the effect of time interval was retrospectively analyzed in a series of patients who had radiotherapy followed by hyperthermia for inoperable cervical cancer. The results of this clinical study, described in Chapter 6 confirm the in vitro data that also in patients the tumor recurrence was higher and their survival was lower when interval times were longer.

**Novel multimodality combinations with hyperthermia**

The purpose of the studies described in the last part of this thesis was to explore if the effects of hyperthermia could be improved by adding agents that specifically target the previously studied DNA-repair pathways. In the study described in Chapter 7, a PARP1-inhibitor was added to cisplatin with hyperthermia; the last combination is clinically given to women with recurrent cervical cancer after previous radiotherapy. The novel combination of chemotherapy, hyperthermia and PARP1-inhibitor resulted both in vitro and in vivo in a more effective therapy. The in vivo studies in rats did not show additional side-effects.

Cisplatin is one of the oldest and most widely applied chemotherapeutic agents, but it can also induce severe and permanent side-effects. Since cisplatin is associated with severe systemic side-effects, such as renal insufficiency and neurotoxicity, the study in Chapter 8 describes the results of experiments wherein the cisplatin dose was reduced in combination with hyperthermia and a PARP1-inhibitor. The addition of a PARP1-inhibitor to hyperthermia and cisplatin demonstrated that PARP1-inhibitor allows a reduction of the cisplatin dose, without decreasing tumor cell death.

Next to the previously described options to improve treatment outcomes with hyperthermia, another opportunity to boost the efficacy of hyperthermia is with a small molecule inhibitor of heat shock protein 90 (HSP90-inhibitor). The HSP90s are upregulated in the heated area and they prevent heat-induced unfolding, inactivation and degradation of many proteins. Therefore, interfering with these counteracting chaperone proteins that protect cells from hyperthermia stress, improves the effect of hyperthermia. Results are shown in Chapter 9. Combination of hyperthermia and HSP90-inhibitor resulted in a high increase of micronuclei, indicating cells enter mitosis with the presence of DNA double strand breaks. In conclusion, addition of HSP90-inhibitor enhances hyperthermic radiosensitization and chemosensitization.

Although most of the treatments described in this thesis can significantly reduce the number of surviving tumor cells, the ultimate objective of cancer therapy is to eradicate all tumor cells. The biggest challenge then is to identify and kill the subset of therapy-resistant cancer cells. This subset of treatment resistant
cancer cells may have the ability to initiate recurrences or metastases and are also referred to as tumor-initiating cells or cancer stem cells. These therapy-resistant cancer cells typically hide in the hypoxic and nutrient deprived areas of the tumor, which are also the locations where ionizing radiation and chemotherapy are the least effective. Then it is important to remember that hyperthermia has been described as an excellent treatment to diminish hypoxia in tumors, thereby changing the hypoxic microenvironment, and the comfort zone of these hypoxic cancer stem cells. In Chapter 10, a combinational treatment including hyperthermia is proposed as a promising strategy to tackle the stem cell niche by sensitizing the therapy-resistant cells and reducing their DNA damage repair capacity.

The work discussed in this thesis did lead to more insight in the working mechanisms of hyperthermia, thus to optimization of the application of hyperthermia in the clinic and to novel promising multimodality treatments. The overall conclusion therefore is that, as tumors cells can’t stand the heat, the effectiveness of cervical cancer treatment can be boosted by hyperthermia.
Discussion

Hyperthermia works. There is mounting clinical and experimental evidence that it does. However, hyperthermia is not regarded a conventional first-line treatment and it is not widely applied in routine clinical practice in spite of the fact that hyperthermia has already been applied since the early 1980s, and with good clinical outcome. Fortunately, hyperthermia continues to be applied and worldwide there is a revival of interest by investigators. What more evidence is needed to convince clinicians and researchers who are sceptic about the benefits of hyperthermia? In the following paragraphs, we wish to summarize what is already known about hyperthermia and what knowledge needs to be improved for acceptance of hyperthermia as a standard modality in anti-cancer treatment.

The current status of hyperthermia

One of the reasons that hyperthermia is disappointingly infrequent applied in the clinic, despite its proven efficacy as the most effective and safe sensitizer of radiotherapy and chemotherapy, may be the insufficiency of a biological rationale or, in other words, the limited understanding how hyperthermia interacts with the relevant cellular processes. It is known that hyperthermia triggers multiple mechanisms through which it sensitizes cells to radiotherapy and chemotherapy. Hyperthermia can inhibit homologous recombination (HR), one of the major DNA double strand break repair pathways, which is accountable for approximately 20% of DNA damage repair in S and G2 phase (Kakarougkas & Jeggo, 2014). At this moment it is unclear whether mild hyperthermia (≤42.5°C) also interferes with the more dominant DNA repair pathway, the non-homologous end joining (NHEJ) (reviewed by (Oei et al., 2015)). In this thesis, the NHEJ is scrutinized, by studying the effectiveness of hyperthermia in HR-deficient cells. As these cell lines lack functional HR, these cells completely depend on NHEJ repair. Our results demonstrate that hyperthermia also affects these cell lines. In these cells a reduction of ligase IV (a protein required for NHEJ) was observed indicating that the NHEJ can also be affected by hyperthermia. This result supports the rationale to include hyperthermia as a standard modality against a wide range of tumors, as the NHEJ is accountable for approximately 80% of the repair of DNA double strand breaks (Kakarougkas & Jeggo, 2014). However, in cells without defects in repair pathways, conflicting results were found. Due to functionality of both repair mechanisms, disruption of HR by hyperthermia does not necessarily lead to massive cell death, but the disruption may be bypassed by shifting DNA repair more towards NHEJ (Bergs et al., 2013). This shift is only partial because the survival after hyperthermia is reduced and because NHEJ also appears to be affected by hyperthermia as our results demonstrated. Therefore, combining hyperthermia with targeting of the NHEJ may further improve effectiveness of hyperthermia (see next paragraph on multimodality treatments).
There have been discussions on whether hyperthermia induces DNA double strand breaks or not (reviewed in Chapter 2), because in several cases, a slight increase in γ-H2AX protein levels is found after hyperthermia alone (Hunt et al., 2007; Kaneko et al., 2005). This is a commonly used marker for DNA double strand breaks. However, it has been suggested that these are false-positive phosphorylated stainings, i.e. γ-H2AX positive, but not indicative for DNA double strand breaks (Laszlo & Fleischer, 2009a; Laszlo & Fleischer, 2009b). The results described in Chapter 3 show, by using another technique (the comet assay), that hyperthermia does not induce DNA breaks shortly after treatment. This confirms the second theory, the phosphorylated proteins which are detected by the γ-H2AX foci staining may be false positive, or other phosphor-sites are stained. Therefore, in our experience, mild hyperthermia itself is not directly effective against tumor cells and hyperthermia as a monotherapy is not an effective anti-cancer therapy. Unfortunately, hyperthermia causes poor outcomes in some commercial hospitals around Europe, where hyperthermia is not combined with radiation or chemotherapy. This undesirable practice may be the reason of the negative connotation that other, more academic clinicians may have about hyperthermia. This can be resolved by promoting evidence-based protocols for the application of hyperthermia, just like any other anti-cancer treatment. We should aim at further development and validation of similar widely accepted protocols for the application of hyperthermia, the validation of these protocols will require large randomized multicenter studies. Currently hyperthermia is only available in a limited number of centers. Availability of reliable hyperthermia equipment and expertise to handle this equipment is limited at this moment. To include as many patients as possible, mobile hyperthermia devices may be an option to increase the number of participating hospitals. This would increase the use and results increasing the evidence based trials. For the long term, more affordable devices should become available. In the end, our expectation is that the results will demonstrate that hyperthermia boosts the effectiveness of conventional therapies when applied in a correct manner. Our confidence in this matter is backed by the presently available positive results from randomized trials from the recent past.

Optimizing protocol: Finding the best sequence and time interval between hyperthermia and radiotherapy
A very important issue in providing the best protocol for hyperthermia and radiotherapy, is finding a consensus on the sequence in which these therapies should be applied. Whereas in the United States hyperthermia is generally applied before radiotherapy, the standard guideline in Europe prescribes hyperthermia after radiotherapy. We found no significant difference between the two sequences of applying heat and radiation in tumor cells lines, tested in vitro experiments. Whether hyperthermia is applied 4 hours before or 4 hours after ionizing radiation results in similar reductions in cell survival, implying that interference with the “slow” DNA repair pathway (HR) by hyperthermia is
a dominant process. This conclusion is logical since the “fast” NHEJ repair takes place within seconds after DNA is damaged and will be finished within a few hours. Therefore, our in vitro data on HR proficient cells suggest that the fast repair is less affected by mild hyperthermia alone. However, as re-oxygenation cannot be studied in in vitro experiments, the issue of the dominant mechanism in a clinical setting remains undecided. Furthermore, this result only concerns tumor cells and not normal tissue toxicity. The optimal time interval and sequence also covers the best balance between targeting the tumor tissue as much as possible, with tolerable damage to the normal tissue. Finally, direct cell death due to radiotherapy and hyperthermia does not give insight in tumor relapse. The in vitro experiments did show more cell death after a shorter time interval, but then again, this has not yet been tested in respect to the normal tissue. Research studying the effects on normal tissue toxicity is ongoing.

The importance of limiting the time interval between radiotherapy and hyperthermia was not only demonstrated in in vitro results. In patients, the optimal window between radiotherapy and hyperthermia to gain a beneficial effect is even shorter. This difference between tumor cells in vitro and patients is that, unlike the situation in human beings, cultured tumor cells are treated under optimal conditions, i.e. the temperature distribution is homogeneous and oxygen levels are perfectly regulated. The clinical lesson to be learned is that shortening the time interval between radiotherapy and hyperthermia is essential in achieving a higher overall survival. A limitation of the patient study was the relatively small number of patients (n=58). Moreover, among all patients with inoperable cervical cancer, these patients even had more dismal prognostic factors, which coincides with their contraindication against receiving chemotherapy. This group included a large number of elderly and physically unfit patients. If hyperthermia becomes a standard treatment for a larger group of patients, the impact of sequence and time interval must be re-evaluated prospectively in a randomized trial which includes patients with various ages and with different physical status. The impact should be compared for patients with different ages and various physical conditions as the sequence and time interval between radiotherapy and hyperthermia might be even more important in younger and physically fitter patients, effects may be larger and perhaps last longer, as the response of blood flow to hyperthermia may be better in younger patients.

**HPV+ tumors, a special target for hyperthermia?**

Remarkably, cervical carcinoma has a favorable clinical outcomes after combinaional therapies including hyperthermia (Datta et al, 2016). In this thesis (Chapter 4), we explored one possible mechanism explaining the success of hyperthermia in this particular tumor type. Whereas hyperthermia interferes with the complex formation of HPV-E6 and p53 in HPV+ cervical carcinoma cell
lines, thereby rescuing p53 to become active and induce tumor cells death, a new logical question rises whether hyperthermia has this effect on all HPV- tumor types, such as anal cancer and tumors of the head and neck. These questions are definitely high ranking on our list of topics to be investigated in future projects. According to our results, hyperthermia is rather unique in interrupting the tumor promoting complex formation of E6 and p53; neither radiotherapy nor chemotherapy, or the combination of both is able to do so. Therefore, it may be important to support clinical application of hyperthermia in all patients with HPV- tumors and not only for a selected group of patients. Whereas cervical carcinoma has a significantly better outcome when combined with hyperthermia, head and neck tumors which are caused by HPV have already been found to respond very well to radiotherapy alone. It would therefore be extremely interesting to investigate if hyperthermia could further increase clinical outcomes for this specific tumor type. Elucidating whether hyperthermia has similar effects in all HPV+ tumor types would be essential, in order to prevent over-treating patients. As there are also multiple investigations testing the effectiveness of hyperthermia in both HPV- and HPV+ head and neck tumors, also in clinical trials, the current clinical outcomes of treated head and neck tumors need to be improved. The effect on E6 is certainly not the only effect of heat. In HPV- tumors hyperthermia induces p53 dependent apoptosis as well. This raises the question whether hyperthermia affects MDM2, which is an important p53 regulator. This issue remains to be investigated.

Hyperthermia to target CSC?
Treatment failure after local radiotherapy and systemic chemotherapy in women with cervical cancer is caused by distant metastases, regional failure and local recurrence. The initial response to treatment is usually favorable, but recurrences still occur, probably caused by a small percentage of cells that become therapy-resistant. These therapy-resistant cells, typically localized in the hypoxic area of the tumor, often show similar characteristics to normal tissue stem cells, and are therefore referred to as cancer stem cells (CSCs). These CSCs have the capacity to re-populate and re-establish an entirely new tumor. In Chapter 10, we argued that hyperthermia targets exactly the areas in which radioresistant cells are located, and may therefore strengthen the forces in the battle against CSCs. Indeed, in tumors located in previously irradiated areas, low doses of radiation combined with hyperthermia proved to be just as effective as high doses of radiation. This protocol is chosen to prevent too much normal tissue toxicity caused by ionizing radiation. Hyperthermia can then be added to prevent cells from becoming radioresistant. It would therefore be interesting to investigate whether hyperthermia can sensitize CSCs to chemotherapy and radiotherapy. In vitro and in vivo experiments are needed to confirm this hypothesis. This could shed light on why hyperthermia can increase the local disease free survival in clinical trials.
This raises the question whether hyperthermia should be applied already in primary tumors to avoid cells from getting therapy-resistant (by reaching all areas of the tumor with the combinational anti-cancer treatment), or whether hyperthermia is more effective when specifically applied to treat when radioresistant cells are known to be present and posing a problem for conventional therapies. The outcome of this debate depends on whether hyperthermia has the ability not only to reduce hypoxia in primary tumors, but more importantly, to make usually well oxygenated recurrences and metastases more vulnerable to conventional therapy by targeting the CSCs. This approach can not only increase tumor response and time to recurrence, but can also increase cancer cure rates, if hyperthermia actually can kill all remaining tumor cells.

Multimodality treatments to improve the effectiveness of hyperthermia
As mentioned before, hyperthermia is not effective as a single modality treatment of cancer, but is very effective after combination with radiotherapy or chemotherapy. If tumor recurrence is located in previously irradiated areas, it is preferred to avoid radiotherapy. Combinational treatments with hyperthermia, cisplatin and PARP1-inhibitors have been investigated in in vitro and in vivo experiments. Once radiotherapy is contraindicated for treatment, hyperthermia and cisplatin is an established combination for retreatment of these therapy resistant tumors. The rationale to combine hyperthermia with PARP1-inhibitors, originates from the induction of synthetic lethality by treating BRCA-deficient cancer cells with PARP1-inhibitors. Since PARP1 plays a crucial role in the repair of single strand breaks, treatment with a PARP1-inhibitor will convert single strand breaks into double strand breaks. These will normally be repaired by HR, in which BRCA-proteins are essential. Therefore, patients who have BRCA1,2-deficient tumors are, theoretically, likely to benefit from PARP1-inhibitor without too much normal tissue toxicity, since only the tumor cells lack functional BRCA. In Chapter 7, rats treated with cisplatin, hyperthermia and PARP1-inhibitor showed a tumor growth control, without observing any side-effects. However, in four different studies (all using Olaparib), a slower tumor progression was found, but patient survival was not improved. Worse, serious side-effects such as nausea, fatigue, vomiting and anaemia were observed (Ledermann et al, 2012; Wiggans et al, 2015). In a fifth study, also treating epithelial ovarian cancer, Veliparib (another PARP1-inhibitor) was used, demonstrating fewer severe side-effects, but the patient numbers were too small to draw any firm conclusions (Wiggans et al, 2015). Either lower doses of PARP1-inhibitors should be applied to reduce side-effects, or the clinical effects of a newer generation PARP1-inhibitors with lower toxicities should be investigated. Since hyperthermia is a local therapy that can temporarily downregulate BRCA2, we argue that hyperthermia creates a time window to treat all tumor types, including BRCA-proficient tumor types.
The trimodality of cisplatin, hyperthermia and a PARP1-inhibitor shows a higher tumor cell death than only thermochemotherapy (Chapter 7). Cisplatin is a very effective and widely used chemotherapeutic agent. However, as cisplatin is used as a systemic therapy, it does not distinguish between tumor cells and fast replicating non-tumor cells as cisplatin targets all fast replicating cells. The - sometimes irreversible - side-effects can be serious, as it can result into hearing impairment, sensory loss and kidney failure. The side-effects can already be reduced by so-called hyper-hydration of the patient before cisplatin is administered. However, hyper-hydration increases the clearance of the drug from the body, and may thereby reduce the effectiveness of cisplatin. As shown in Chapter 8, the addition of a PARP1-inhibitor to hyperthermia and reduced cisplatin levels, is equally effective as standard cisplatin dose with hyperthermia. This finding can be clinically interesting to maintain tumor control at reduced cisplatin, thereby reducing severe and irreversible toxicity. Moreover, it would also be interesting to evaluate if addition of PARP1-inhibitor can compensate for hyperthermia treatment at a lower temperature, or a high temperature for a shorter treatment time.

Another approach to boost the effectiveness of hyperthermia is achieved by interfering with counteracting chaperone proteins (for example Heat Shock Proteins, HSPs) that protect cells from hyperthermia stress. Several in vitro and in vivo studies demonstrate targeting of HSPs combined with other anti-cancer treatments, can improve treatment outcome (Ciocca et al, 2010). Also, promising results are shown in clinical trials (Calderwood, 2010). As the effects of hyperthermia were temporary, a simultaneous application of HSP inhibitor would be required for further boosting effectiveness of HT. In vivo studies are the first step towards clinical application, and when results are positive this may eventually encourage to start clinical trials to validate these novel multi-modality strategies. A particularly important question is evaluation of the toxicity profile of the proposed multi-modality schedules. For instance, stress factors like hyperthermia, chemotherapy and radiotherapy can induce HSPs. As HSP90 regulates protein folding, prevents misfolding and assists in the function of various proteins, also in healthy cells, inhibition of this protein may result in some toxicity.

**Future perspectives for hyperthermia in cervical carcinoma**

The Dutch Deep Hyperthermia Trial (van der Zee et al, 2000) demonstrated significant increased tumor control and survival benefit if hyperthermia was added to radiotherapy in cervical carcinoma. In this trial, radiotherapy was compared to radiotherapy combined with hyperthermia in patients with advanced bladder, cervical and rectal tumors. In cervical cancer patients, the complete response rate was significantly higher after radiotherapy combined with hyperthermia (83%) compared to radiotherapy alone (57%). Similar results were reported in other randomized trials evaluating the effect of combining...
hyperthermia and radiotherapy in cervical carcinoma.

However, the current standard treatment of patients with locally advanced cervical cancer is not radiotherapy alone, but cisplatin based chemoradiotherapy. In the RADCHOC trial (Lutgens et al., 2016), hyperthermia combined with radiotherapy was compared to chemoradiotherapy, and did not show a significant difference between the two approaches. It should be noted that many patients in the RADCHOC trial received radiotherapy in the nearest radiotherapy facility, but had to travel sometimes several hours to receive hyperthermia in a distant facility. In our retrospective patient series, described in Chapter 6, we discovered that a long time interval between radiotherapy and hyperthermia is detrimental for treatment outcome, and that the time interval between the two modalities should preferably be as short as possible, mandating delivery of both in the same facility. Then, the outcome of thermoradiation may eventually be much better as was suggested by the RADCHOC study.

Taking it to the next level, standard chemoradiotherapy versus hyperthermia plus chemoradiotherapy has also been investigated in a multicentre randomised clinical trial in Japan in locally advanced cervical carcinoma (Harima et al., 2016). A trend was seen demonstrating a higher five-year overall survival of 77.8% in the arm treated with hyperthermia and chemoradiotherapy vs. 64.8% for chemoradiotherapy alone. Complete response rates were significantly higher when hyperthermia was added to chemoradiotherapy (88% vs. 77.6%). Moreover, the triple modality was well tolerated, no additional toxicities were observed. A comparable multicentre trial randomizing between the same two arms, initiated from Duke University Medical Center, the Academic Medical Centre Amsterdam, and other international partners (Westermann et al., 2012) did show a non significant trend towards a benefit of adding hyperthermia to chemoradiation regarding local control (70% to 78%) but no benefit regarding overall survival. The latter may be due to a considerable number of patients that had para-aortic lymph node metastases beyond the heated region of the primary tumor. This warrants the development of hyperthermia techniques capable of safely heating even larger volumes, or to target the para-aortic lymph nodes separately.

Considering the cytotoxicity to the normal tissue due to cisplatin-based treatment, the rationale to prefer hyperthermia over cisplatin or to give trimodality treatment with a significantly reduced cisplatin dose seems logical. Further clinical studies to confirm these data are warranted.

Multiple clinical trials are under investigation. For example, a clinical trial is ongoing at the University of Texas Health Science Center, in which the effectiveness of triple-modality treatment for inoperable or metastastic pancreatic cancer is investigated (www.clinicaltrials.gov). Also, clinical trials in which combinational treatments of hyperthermia with PARP1-inhibitor are explored.
In conclusion, hyperthermia is a local treatment, which has proven its effectiveness in multiple clinical trials (Datta et al., 2016) and still many new improvements are explored. Not only did several studies demonstrate favorable clinical outcomes, in none of the patients severe toxicities were reported associated with hyperthermia. A good treatment not only targets the tumor cells, it must also spare the normal tissue as much as possible to reduce toxicity, both to prolong life and maintain a good quality of life for patients after treatment. After elucidating the mechanisms responsible for the effectiveness of hyperthermia, application in clinical practice of hyperthermia may be improved, which hopefully is a step towards routine clinical practice for all patients who may benefit from hyperthermia as I feel hyperthermia is potentially beneficial for a much larger group of patients than the relatively small number of patients who are presently treated with hyperthermia.
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