The role of hyperthermia in the treatment of locally advanced cervical cancer: a comprehensive review

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ABSTRACT
Radiotherapy with cisplatin (chemoradiation) is the standard treatment for women with locally advanced cervical cancer. Radiotherapy with deep hyperthermia (thermoradiation) is a well established alternative, but is rarely offered as an alternative to chemoradiation, particularly for patients in whom cisplatin is contraindicated. The scope of this review is to provide an overview of the biological rationale of hyperthermia treatment delivery, including patient workflow, and the clinical effectiveness of hyperthermia as a radiosensitizer in the treatment of cervical cancer. Hyperthermia is especially effective in hypoxic and nutrient deprived areas of the tumor where radiotherapy is less effective. Its radiosensitizing effectiveness depends on the temperature level, duration of treatment, and the time interval between radiotherapy and hyperthermia. High quality hyperthermia treatment requires an experienced team, adequate online adaptive treatment planning, and is preferably performed using a phased array radiative locoregional hyperthermia device to achieve the optimal thermal dose effect. Hyperthermia is well tolerated and generally leads to only mild toxicity, such as patient discomfort. Patients in whom cisplatin is contraindicated should therefore be referred to a hyperthermia center for thermoradiation.

INTRODUCTION
Cervical cancer is the fourth most common cancer in women worldwide, especially in underdeveloped countries, 1 with approximately 570 000 new cases of cervical cancer and more than 300 000 deaths from this malignancy in 2018. 1 Cervical cancer most often arises from a persistent infection with the cancer causing human papillomavirus types 16 and 18. 2 Radiotherapy with cisplatin based chemotherapy as a radiosensitizer (chemoradiation) is the standard treatment for women with locally advanced cervical cancer. 3 Radiotherapy with deep hyperthermia is a well established alternative. Hyperthermia is a technique that already gained interest in the field of medicine in 1898 by Frans Westermark; he was the first physician to use local tumor heating to treat cervical cancer, by circulating heated water through a metal coil. 4 His work was carried on by his son, Nils Westermark, who hypothesized that tumor tissue would be more heat sensitive than healthy tissue. 4, 5 In the 1930s, radiologist Kristian Overgaard experimented with the combination of hyperthermia and radiotherapy (thermoradiation), and showed better tumor control with thermoradiation compared with radiotherapy alone. 6 Hyperthermia, defined by local heating of the tumor up to 42°C for approximately 60 min, has been used as an alternative radiosensitizing treatment in women in whom cisplatin is contraindicated for the treatment of gynecologic cancers, such as vaginal and cervical cancer. 6 Even though deep hyperthermia has been widely accepted as a radiosensitizer, hyperthermia is rarely offered as an alternative to cisplatin. Despite the evidence, carboplatin is most often offered as an alternative to cisplatin, even though there is less evidence that this works equally well. 7

The aim of this article is to provide an overview of the clinical data of the effectiveness of hyperthermia as a radiosensitizer through deep hyperthermia in cervical cancer patients, the biological rationale supporting its use, and the patient workflow and equipment used.

SEARCH STRATEGY AND SELECTION CRITERIA
A systematic literature search was conducted to obtain an overview of the existing evidence of hyperthermia in the treatment of cervical cancer. The inclusion criteria were: original clinical studies published after 2000, written in English, and a minimum of 40 included patients. In addition, only studies with a curative intent were included. If the same patient cohort was reported in more papers, only the most recent publication was included. Finally, a reference cross check was performed. Searches in PubMed were performed with the following search terms: “((cervical cancer, uterine(MeSH Terms)) AND (hyperthermia, induced(MeSH Terms)))” OR “((cervical cancer, uterine(MeSH Terms)) AND (radiotherapy(MeSH Terms)) AND (hyperthermia, induced(MeSH Terms)))” OR “((cervical cancer, uterine(MeSH Terms)) AND (radiotherapy(MeSH Terms)) AND (hyperthermia, induced(MeSH Terms)) AND (cisplatin(MeSH Terms)))” OR “((cervical cancer, uterine(MeSH Terms)) AND (radiotherapy(MeSH Terms)) AND (hyperthermia, induced(MeSH Terms)) AND (cisplatin(MeSH Terms)))” OR “((cervical cancer, uterine(MeSH Terms)) AND (radiotherapy(MeSH Terms)) AND (hyperthermia, induced(MeSH Terms)) AND (cisplatin(MeSH Terms)))”.

RADIOBIOLOGICAL BACKGROUND
Hyperthermia and cisplatin are potent radiosensitizers. Both are used to increase the cytotoxic effects...
of ionizing radiation on cancer cells. Radiotherapy and cisplatin based chemotherapy aim to cause lethal DNA damage, where DNA double strand breaks are considered the most lethal. Ionizing radiation induces DNA double strand breaks directly and indirectly. Induction of DNA breaks immediately triggers DNA double strand break repair pathways. There are two main DNA double strand break repair pathways: homologous recombination and non-homologous end joining. Hyperthermia can temporarily inhibit DNA repair via the homologous recombination pathway and the non-homologous end joining pathway, resulting in accumulation of unrepaired DNA breaks. The effectiveness of hyperthermia is dependent on the temperature level, duration of treatment, and the time interval between radiotherapy and hyperthermia. Evidence suggests that simultaneous radiotherapy and hyperthermia give the highest enhancement, and the time interval between hyperthermia and ionizing radiation should therefore be kept as short as possible, preferably within 1 hour. Longer intervals will lead to impaired inhibition of DNA repair due to less effectiveness of the hyperthermia, and will consequently lead to increased tumor cell survival. Even though others found no significant differences within 1–4 hours, close analysis suggests that the time interval should not exceed 1 hour for full exploitation of the hyperthermia effects. Some clinical protocols for breast cancer apply nearly 1 hour...
simultaneous ultrashort 5 min time intervals between hyperthermia and radiotherapy, however, such short intervals are not feasible in cervical cancer treatment.22

HYPERTHERMIA: TECHNICAL ASPECTS AND PATIENT WORKFLOW

Hyperthermia Devices
The hyperthermia devices currently used for locoregional treatment of deep seated tumors, including cervical cancer, use electromagnetic energy and can be subdivided in two types of systems, radiative and capacitive. Radiative heating devices are phased arrays of 4–12 antennas positioned around the pelvis of the patient, operating at 70–150 MHz.23 Capacitive heating devices operate at 8–13 MHz and use two electrodes placed on the ventral and dorsal side of the pelvis. For both devices, a cooled water bolus is placed between the antenna or electrode and the skin to prevent overheating of the skin. Adequate therapeutic tumor temperatures are more easily achieved using radiative devices due to the risk of treatment limiting excessive skin temperatures when using capacitive devices, particularly when the subcutaneous fat layer thickness exceeds ~1 cm.24 25 European Quality Assurance guidelines thus recommend use of radiative phased array devices for patients in the Western world.26 Hyperthermia treatment delivery requires online temperature monitoring and online adaptation of system settings in response to low tumor temperatures or patient complaints when treatment limiting normal tissue hot spots occur. Online temperature monitoring is performed using minimally invasive temperature probes, typically inserted in the bladder, vagina/cervix, and rectum. Application of non-invasive MRI thermometry is under development for treatment of deep seated pelvic tumors, but patient size and motion artifacts are currently limiting factors for its application and accuracy.27 Locoregional heating implies that temperatures in neighboring organs, such as the bladder and rectum, are also raised to elevated levels; this is considered acceptable as hyperthermic radiosensitization is tumor selective and provided temperatures do not exceed 44–45°C. Treatment planning is currently used in select academic centers28 where real time (online) adaptive planning is quantitatively reliable.28

Patient Workflow
The workflow for delivery of locoregional hyperthermia treatment involves several steps.29 First, hyperthermia should be planned in sequence with radiotherapy delivery. In general, hyperthermia is given once a week shortly before or after the radiotherapy fraction. In some exceptions, hyperthermia is given twice a week, with at least 3 days in between each session to avoid induction of thermotolerance.30 To achieve the maximal benefit of hyperthermia as a radiosensitizer, the time interval between radiotherapy and hyperthermia should be less than 1 hour.18 In our center, after placement of minimally invasive catheters for insertion of temperature probes in the vagina, bladder, and rectum, a hyperthermia planning CT is made of the patient on the hyperthermia mattress and water bolus around with these thermal probe catheters in situ (Figure 2A). This CT is used for automatic segmentation of high versus low water content tissue for hyperthermia treatment planning, where the tumor is contoured by the physician, guided by the MRI made for radiotherapy planning (Figure 2B). In addition, the CT is used for establishing which temperature measurement points represent tumor and which normal tissue for optimal temperature control during treatment. The aim of the hyperthermia treatment planning is to determine...

Figure 2  Hyperthermia treatment planning and temperature during treatment. (A) Hyperthermia treatment planning with the cervical tumor contoured in red on a dedicated hyperthermia CT scan with thermal probes in situ made directly before hyperthermia treatment. Also shown are the hot (red area) and cold (green area) spots. (B) MRI scan as help for appropriate contouring of the tumor on CT. (C) Real tumor temperature profile containing temperature readings of target area and surrounding areas during treatment. (D) Simplified tumor temperature profile during treatment.
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After CT, the patient is transported to our deep hyperthermia facility and treatment starts. Multi-sensor temperature probes are inserted into the thermal probes in the vagina, bladder, and rectum. The patient lies on a mattress with four antennas placed around the target volume (Figure 3). To avoid skin burns, water cooling boluses are placed between the antennas and the skin of the patient. Next, the patient is positioned in the system with the tumor at the center of the antenna ring, based on the tumor location on the CT. Minimally invasive temperature monitoring by temperature probes in the cervix, bladder, and rectum is mandatory, and can in selected cases be supplemented with non-invasive MRI based thermometry when using a hybrid locoregional hyperthermia system. Power is switched on and the heating up period starts (~15–30 min) (Figure 2C,D). When a tumor temperature of 41°C is reached, the 1 hour steady state period starts (Figure 2C,D). Operators continuously monitor the temperature readings and patient comments during treatment, and re-optimize device settings when needed in response to suboptimal tumor temperatures, treatment limiting hot spots, or patients feeling too uncomfortable. This continuous real time monitoring and re-optimization, also guided by adaptive hyperthermia treatment planning, yields optimal tumor temperatures. However, to be able to deliver such a high quality hyperthermia treatment, an experienced, well trained team is crucial to reach the optimal thermal radiosensitizing effect. A higher thermal dose can be achieved both by increasing the temperature or by extending the treatment time, where locoregional hyperthermia treatment of 1 hour is considered the maximum patients can tolerate.

Figure 3  Locoregional radiative hyperthermia device: the example shown here is the four antenna ALBA4D system. (A) Photo and drawing of the front with a patient in position showing the cranial and lateral antennas and the water bolus between the patient and antennas. (B) Photo and drawing from the side, showing that the bottom antenna and a second water cooling bolus is positioned below the patient. (C) Photo and drawing from behind with a patient in position, showing the water cooling boluses on all four sides and the position of the thermometry systems and thermometry probes. a, antenna, wb, water cooling bolus.
The combined treatment was well tolerated and no additional
hyperthermia related toxicity was seen in the thermoradiation
(43). Notably, the majority (62%) of patients had FIGO stage III disease
versus 27%, respectively, in favor of the thermoradiation group.

The older studies, before the introduction of cisplatin as a sensi-
tizer, compared radiotherapy with hyperthermia (ther-
otherapy versus radiotherapy alone). In 2000, the
trial published in 2005, showed no benefit from ther-
otherapy, compared radiotherapy with hyperthermia. In 2000, the
terapy and radiotherapy combined with hyperthermia (ther-
otherapy vs radiotherapy).37, 38, 39 one study compared chemoradiation with ther-
otherapy and radiotherapy,34 35 three studies compared chemoradiation with ther-
otherapy vs radiotherapy alone. It seemed, however, that the
results of the Dutch Deep Hyperthermia trial were published.40 This
in this multicenter study was that inadequate hyper-
thermia techniques and quality assurance were applied, and that

A comment on this multicenter study was that inadequate hyper-
thermia techniques and quality assurance were applied, and that

Another randomized trial with 40 patients also showed a signifi-
cant difference seen in severe (grade 3) acute and late toxicity.

Table 1 Summary of patient and treatment characteristics, and treatment outcomes of the included randomized controlled trials. Outcome data are expressed at 5 years, unless indicated differently.

| Author (year of publication) | Years of inclusion | No of patients | Mono/ multi center | Treatment arms | Median FU (months) | Age (years) | FIGO stage (n %) | HT device | HT temp (median °C) | Outcome |
|----------------------------|-------------------|----------------|-------------------|----------------|-------------------|------------|-----------------|-----------|------------------|---------|
| Harima (2001)29             | 1994–1999         | 40             | Mono              | RT vs RHT      | 36                | 62 vs 65    | 0 (0)           | 0 (0)     | 0 (0)            | 10 vs 10 |
| Van der Zee (2002)10        | 1990–1996         | 114            | Multi             | RT vs RHT      | 43                | 56 vs 58    | 0 (0)           | 22 (19)   | 81 (71)          | 0 (0)    |
| Vasanathan (2005)           | 1998–2002         | 110            | Multi             | RT vs RHT      | 16                | 50 vs 45    | 0 (0)           | 56 (51)   | 51 (46)          | 3 (3)    |
| Lutgens (2016)27            | 2003–2009         | 84             | Multi             | CRT vs RHT     | 85                | 53          | 18 (21)         | 46 (55)   | 18 (21)          | 2 (3)    |
| Harima (2018)33             | 2001–2015         | 101            | Multi             | CRT vs RHT     | 55                | 62 vs 60    | 1 (1)           | 26 (26)   | 66 (65)          | 8 (8)    |
| Minnaar (2019)28            | 2014–2017         | 202            | Mono              | CRT vs RCHT    | 6                 | 49 vs 48    | 0 (0)           | 75 (36)   | 2 (1)            | 129 (63) |
| Wang (2020)39               | 2009–2013         | 373            | Mono              | CRT vs RCHT    | 60                | 50 vs 51    | 7 (2)           | 230 (62)  | 127 (34)         | 0 (0)    |
| Bold type indicates significant difference. *Based on 3 years of follow-up. †Based on 7 years of follow-up. ‡Based on 6 months of follow-up. CRRT, chemoradiation with hyperthermia; DFS, disease free survival; FIGO, International Federation of Gynecology and Obstetrics 2008; FU, follow-up; HT, hyperthermia; LC, local control; NA, not available; OS, overall survival; PC, pelvic control; RCHT, chemoradiation with hyperthermia; RT, radiotherapy; Hyperthermia.
the reported temperatures overestimated the tumor temperature achieved.43

Three randomized trials comparing radiotherapy with thermorad-
iation were not found by our search because the results were
published in non-English journals. Data from these studies were,
however, included in a Cochrane review about the combined use of
hyperthermia and radiotherapy in locally advanced cervical cancer
patients.44 This review included six randomized studies published
from 1987 to 2009, and showed better outcomes with the addition of
hyperthermia to radiotherapy.44 Pooled data analysis showed a
significantly higher local response rate, and better 3 year local
control and overall survival. No differences were seen in acute and
late severe toxicity. Notably, 74% of the included patients had FIGO
stage III disease.

Only one randomized trial compared chemoradiation with ther-
moregulation in women with bulky and/or FIGO stage ≥III cervical
cancer.37 This study was prematurely closed due to a lack of
accrual. In total, 84 patients were enrolled.37 No significant differ-
ences in disease free survival and overall survival between the two
treatment arms were found. Although the study was prematurely
closed, these results suggest that thermoregulation yields clinical
outcomes comparable with outcomes of chemoradiation in the
treatment of locally advanced cervical cancer.

Recently, the results of three randomized controlled trials
comparing chemoradiation with chemoradiation in combination
with hyperthermia were published. The first study from Harima
et al (2016) described the results of a multicenter study of 101
patients.42 Although no significant differences in disease free
survival, overall survival, or complete response were seen, the triple
therapy arm performed consistently better than the chemoradia-
tion arm with a gain of all outcome parameters of approximately
10%. The relatively small sample size combined with the fact that
some of the patients received a low suboptimal hyperthermia dose,
likely explains the non-significant difference. More detailed anal-
ysis by Ohguri et al (2018) showed that 5 year disease free survival
was 81% for patients in whom a high thermal dose was achieved
(CEM43T90 ≥1 min) compared with 61% for patients receiving
chemoradiation alone (p=0.036).36

A much larger randomized controlled trial of 435 patients
showed significantly better overall survival in the triple therapy
arm; 5 year overall survival was 82% and 72% for chemoradiation
with hyperthermia and chemoradiation, respectively.38 39 The dif-
ference in relapse free survival was not significantly different. Again,
no difference in acute and late toxicity was seen. Finally, Mimaar
et al (2019) published the preliminary results of their randomized
study in which 271 patients were included.34 They showed a signif-
ificant benefit of adding hyperthermia to chemoradiation regarding
disease free survival, but not overall survival. This might be due to
the short median follow-up period of 6 months.34 Notably, the
results of chemoradiation arm in this study appear to be worse than
expected according to current standards. This is probably because
the study reports the results of cervical cancer care for advanced
stage patients with a relatively poor health status in a low income
country with limited resources to treat patients according to best
practice standards with external beam radiation therapy combined
with chemotherapy, followed by a brachytherapy boost.

A recent meta-analysis concluded that there was a signifi-
cant benefit of adding hyperthermia to chemoradiation for overall
survival, but not for local recurrence free survival. Reassuringly, no
increase in toxicity was seen with the addition of hyperthermia.45

The previously mentioned chemoradiation with hyperthermia
studies all used the easier applicable capacitive hyperthermia
device, however, with the cost that it is more challenging to achieve
the desired tumor temperature levels. The relevance of an optimal
dermal dose was corroborated by a re-analysis of the previously
mentioned study by Harima et al (2001). Ohguri et al (2018) found
that disease free survival was only better in patients in whom a
higher thermal dose was achieved (CEM43T90 ≥1 min) compared
with patients receiving chemoradiation alone.25 Although triple
chemoradiation with hyperthermia therapy may have additional
value over chemoradiation, it is presently not considered as stan-
dard of care in the treatment of locally advanced cervical cancer.
Interestingly, a recent network analysis identified radiotherapy and
hyperthermia, chemoradiation with hyperthermia, and chemora-
diation with 3 weekly cisplatin as the best therapeutic modalities
for the treatment of locally advanced cervical cancer, comprehen-
sively meeting key clinical endpoints regarding tumor control,
overall survival, and morbidity.46 This should, however, be subject to further
research because the current standard chemotherapy regimen is
with weekly cisplatin 40 mg/m².

The results of the three cohort studies included in our review
are summarized in Table 2. Two cohort studies were retrospective
in nature, while one study was prospective. Frackenla et al (2009)
investigated the relationship between thermal dose parameters
and the outcomes disease specific survival, pelvic control, and
complete response rate. They showed that two different thermal
dose parameters both reflecting median tumor temperature and
duration of heating, TRISE (p=0.002 for disease specific survival;
p=0.021 for pelvic control; and p=0.027 for complete response),
and CEM43T90 (p=0.001 for disease specific survival; p=0.019
for pelvic control; and p=0.195 for complete response) were inde-
pendent prognostic factors for tumor control.47 The association
between median thermal dose and outcome was confirmed in a
later study by Kroezen et al.32 They showed that thermal dose also
had a beneficial effect on local control in patients treated according
to the current standards with external beam radiation therapy
followed by MRI guided brachytherapy.32

Finally, Westermann et al (2012) published the long term results
of triple therapy (chemoradiation with hyperthermia) in locally
advanced cervical cancer patients and concluded that this combi-
nation of therapy is feasible, well tolerated, and comparable with
the results of randomized trials at that time. However, since it was
a non-randomized study, no further conclusions could be drawn.48

Carboplatin monotherapy is often offered as an alternative radio-
sensitizer to cisplatin in the treatment of locally advanced cervical
cancer, even though there is no evidence that this works equally
well. Moreover, no clinical trials comparing hyperthermia and radio-
therapy with carboplatin and radiotherapy have been conducted
or planned. However, a few small clinical studies investigated the
effect of combining carboplatin monotherapy with hyperthermia and
radiotherapy.49 50 One phase I study used a combination of radio-
therapy, hyperthermia, and intra-arterial carboplatin in 15 cervical
cancer patients with a local recurrence.49 Although this regimen
was well tolerated, the results were disappointing. Another phase
II study evaluated the effect of whole body hyperthermia in combi-
nation with carboplatin in 25 patients with recurrent or metastatic
Considerable toxicity was seen and the results were comparable with chemotherapy only, and thus this regimen was considered as less suitable in these palliative patients.

Some studies only reported the intended temperature level without measuring temperatures to verify whether the goal temperature was actually achieved. The fact that two different types of hyperthermia systems were used (capacitive and radiative) may also have influenced outcome, because achieving the targeted temperature is more challenging for capacitive devices. All of the included studies in Europe used radiative hyperthermia systems, while many non-European studies used capacitive hyperthermia systems.

Good hyperthermia treatment delivery requires a team of well-trained and experienced professionals, dedicated treatment protocols, reliable hyperthermia devices, and treatment planning and quality assurance. Lack of these has been a cause for failure in some clinical trials and an impediment for wider clinical use of hyperthermia.

In the past decade, hyperthermia systems have improved and guidelines have been developed. Fortunately, reliable treatment planning tools enabling real-time adaptive treatment planning are becoming available. A group of European centers are developing multicenter prospective registration studies with well-designed quality assurance and data reporting for several tumor sites in the framework of the European H2020 ‘Hyperboost’ project (www.hyperboost.eu). These developments will help new users to more easily adopt and apply clinical hyperthermia.

In the studies included, toxicity was generally graded according to the toxicity criteria for adverse events. Although no additional severe toxicity was seen in the hyperthermia trials, hyperthermia can lead to acute and late toxicities in some cases. Thermal burns and fat necrosis in particular are considered hyperthermia-related toxicities, and can be burdensome for the patient. Myopathies and patient discomfort can be seen during and shortly after a hyperthermia session. The risks of hyperthermia-related toxicities can, however, be limited when following good quality assurance protocols.

Although currently patient-reported outcome measures are often used to assess the burden of the treatment on quality of life, no patient-reported outcome measures were assessed in the previously mentioned hyperthermia trials. Expert opinion is that thermoradiation is more tolerable than chemoradiation and could therefore be offered to fragile patients who are unfit for chemotherapy. The typical patients referred for hyperthermia are those who have contraindications to cisplatin. These include women with poor kidney function and hearing loss, but also the elderly and frail patients. In addition, patients who refuse chemotherapy can also be referred for hyperthermia treatment.

FUTURE PERSPECTIVES AND CONCLUSIONS

Radiative locoregional hyperthermia devices are currently optimal for achieving therapeutic temperatures in deep seated tumors, such as in cervical cancer. A novel approach based on induction of hyperthermia by scanning a high intensity focused ultrasound beam through the tumor volume is under development, but its use in humans needs to be tested. Reliable hyperthermia delivery also requires real-time temperature monitoring using minimally invasive temperature probes.
inserted in the vagina/cervix, bladder, and rectum. Non-invasive MRI based thermometry is under development, but its accuracy is presently still strongly limited by motion artifacts, and about half of the patients do not fit into the small bore of the hybrid MRI guided locoregional hyperthermia device.

Pretreatment planning is another valuable tool for optimizing treatment delivery. Treatment planning is currently qualitatively reliable and able to establish system settings reliably targeting the tumor. Real time online adaptive planning during treatment is key in re-optimizing settings during hyperthermia treatment for optimal tumor temperatures and suppression of potential treatment limiting normal tissue hot spots. Commercially available adaptive treatment planning software is under development, including VEDO and Plan2Heat, which allow planning based real time steering during treatment. These tools allow novice hyperthermia users to quickly gain good treatment control. Immunotherapy combined with chemotherapy and radiotherapy is increasingly investigated in cervical cancer trials, and has especially been explored by others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

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In conclusion, cisplatin combined with radiotherapy is the current standard treatment for patients with locally advanced cervical cancer. However, thermoradiation is the best evidence based, well tolerated alternative and should be offered to all patients with contraindications to cisplatin.

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