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Review

Hyperthermia in cervical cancer – current status

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ABSTRACT

Background: This article reviews the salient features of recent results of clinical studies. It puts a special emphasis on technical aspects, mechanisms of action together with radiotherapy and chemotherapy and points out areas for additional investigation.
Aim: To present the current state of knowledge on hyperthermia (HT) and to highlight its role in the treatment of cervical cancer.
Materials and methods: The literature on the clinical use of combined hyperthermia for cervical cancer was analyzed. Clinical outcomes together with the technical aspects and the role of HT were also evaluated.
Results: Clinically randomized trials have demonstrated benefit including survival with the addition of hyperthermia to radiation or chemotherapy in the treatment of cervical cancer without significant acute or late morbidities. The technological advances have led to an effective and safer treatment delivery, thermal treatment planning, thermal dose monitoring and online adaptive temperature modulation.
Conclusions: Due to rapid development over the last decade of hyperthermia systems and new studies at the basic science and clinical level, the perception of hyperthermia as a part of multimodality treatment in cervical cancer has been changed. However, there is still a need for multicentre randomized clinical trials.

1. Introduction

Cervical cancer represents a serious oncology problem in developing countries where 85% of 500,000 cases are diagnosed worldwide. Cervical cancer (CC) accounts for approximately 13% of all cancer cases in women.[1] The highest risk is observed in Africa and South America.[1,2] The global incidence have been decreasing for more than a decade in developing countries as a result of both better diagnosis and better prevention by using vaccines against human papillomavirus (HPV) which are increasingly available. But still, with cancer diagnosed at a regionally advanced stage, prognosis is much worse. In this respect, little progress has been observed in treatment results in recent years. Approximately 54% of patients worldwide continue to be diagnosed at a locoregionally advanced or metastatic stage and the five-year relative survival (relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer) for regionally advanced cervical cancer is 57%.[2] Radiochemotherapy (RTCT) is a standard procedure in locally

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advanced cervical cancer (LACC). That treatment modality is commonly accepted worldwide according to guidelines of many oncology societies, based on randomized study results that have illustrated its advantages as compared to radiotherapy alone.[3–7] Hyperthermia (HT) in the treatment of LACC improves the results of treatment in many studies and analyses, but it is still rarely used by oncologists.

The aim of this article is to present the current state of knowledge on HT and its role in the treatment of cervical cancer.

2. How does HT work?

HT is an intended artificial increase of temperature over the temperature of human body within the range of 39–43 °C. Many laboratory tests have shown how hyperthermia acts on cells and tissues. Certainly, these should not be implemented directly to clinical practice, but they do indicate ways and points of reference for HT that enable us to obtain an additive effect together with RT and CT. Temperature can be raised by applying various electromagnetic waves (including microwaves, radio waves) or acoustic waves (ultrasound). One of the new developments in this area are works on the use of nanoparticles which, when evenly spread in the tumour, may distribute heat homogeneously. However, the source of energy will depend primarily on the type of cancer and its location (superficial vs. deep). Local and regional hyperthermia is used in the treatment of cervical cancer. The former is applied in intracavitary and interstitial delivery of heat for tumours of up to 5–6 cm in diameter. That method is now most commonly combined with interstitial brachytherapy. The other method involves the increase of temperature in a large volume of tissue, e.g. in the pelvis region.[8] Regional hyperthermia also includes HIPEC, during which a cytostatic is administered intraperitoneally under conditions of increased temperature. The other kind of therapy is effectively used against cancers located within the peritoneal cavity, such as pancreatic or colorectal cancer.[9,10] Currently, in locoregional deep HT systems, particularly in LACC, the target volume is treated with external HT using electromagnetic waves. Some progress has also been achieved in high focused ultrasound (HIFU).

The hyperthermia-induced cytotoxic reaction is mainly targeted to proteins. HT reinforces and complements the cytotoxic effect of radiotherapy. This arises from the fact that cells in the S phase are radioresistant but sensitive to HT. Similarly, in anaerobic conditions with low pH, the resistance to radiotherapy grows, but not to HT. Pathogenesis of anoxic areas in tumour is of a multivariate nature, abnormal microcirculation being one of the reasons. HT effects include increased perfusion, induction of apoptosis, e.g. through the BAX protein, reoxidation.[11–13] Finally, HT inhibits the repair of both sublethal and potentially lethal damage by deactivation of key DNA repair pathways.[14]

A very interesting and beneficial mechanism triggered by HT within the scope of clinical use, i.e. 40–42 °C, is the modulation of the immunological system.[15,16] HT causes the growth in the number of Heat Shock Protein 70 (HSP70) on the surface of the cells and in release of HSP70 from tumour cells, which is a call sign for activated NK cells. Dendritic cells are activated through the class I MHC complex to migrate to lymph nodes where they initiate lymphocyte T cytotoxicity towards HSP presenting cells. HT boosts the maturation and migration of dendritic cells and the release of cytotoxins.[17,18]

Chemotherapeutics may act independently, additively or synergistically in combination with HT. The first group include 5-flurouracil, methotrexate, taxans. Among drugs which cause the cell survival curve to change with the growing temperature with an additional cytotoxic effect are doxorubicin, cyclophosphamide, ifosphamide, gemcitabine. In the case of cisplatin (CCDP) and analogues (e.g. carboplatin), a strong effect of hyperthermia on cytotoxicity has even been demonstrated in relatively low temperatures (40.5 °C). The group of drugs producing a synergistic effect also includes bleomycin.[19] The synergy involves an enhanced uptake of the drug in cells, increased production of radicals, increased DNA damage and inhibition of DNA repair, as well as reversal of drug resistance mechanisms.[10,20]

There have been extensive studies to assess the pretreatment HPV levels and how they change during radiotherapy in head and neck cancers. It turned out that similar observations apply to cervical cancer. HPV titer reduction during treatment is a survival predictor, while retaining infection leads to cancer growth.[21] In vitro studies have shown that the temperature of 42 °C degrades protein E6 (oncoprotein, early protein 6 E6) which connects with p53 and mediates its degradation. Therefore, neutralization of E6 protein may prove a promising treatment method to eliminate HPV-positive cancer cells, thus preventing the E6-p53 complex from forming and enabling p53-dependent apoptosis and G2 phase arrest.[22]

3. HT treatment planning and Quality Assurance

Hyperthermia as a method of cancer treatment has often been ignored and avoided. The main factors to hinder clinical use included difficulties in reproducing appropriate temperature in the tumour mass and surrounding tissue, difficulties in precise temperature measurement and, frequently, the lack of protocols of HT used. Due to the diversity of equipment used to increase temperature in the body, direct comparative analysis between treatment centres is often impossible. Measurements during HT are significant.

The technological progress has now enabled the use of state-of-the-art methods, such as fluency maps for temperature distribution at the site of locoregional hyperthermia, specification of temperature at particular regions. Works are also being carried out to provide possibilities to monitor areas receiving adequate dose in Gy and corresponding temperature measurement – the same as during RT planning. Thus, temperature distribution can be planned in 3D and calculate it in real time, preferably with MRI monitoring.[17] Requirements for hyperthermic treatment planning have been gathered in the Quality Assurance Guidelines.[23,24] The T90 indicator is a relevant parameter in optimizing treatment. It is temperature exceeded in 90% of the target volume surface. That parameter has been proved to correlate with clinical outcome. With precise knowledge of temperature levels, treatment plans can be adapted based on expected enhancement effect. In

bimodality treatment, the enhancement effect resulting from the addition of HT can then be calculated and the whole treatment process optimized: RT dose combined with temperature measurement. In order to quantify the synergistic effect of heat and radiation, the Thermal Enhancement Ratio (TER) is used. TER defines the amount of thermal radiosensitivity growth by survival fractions (SFs) after a stand-alone radiotherapy fraction and combined with hyperthermia.[25] The degree of cytostatic radiosensitivity may also be represented as TER which is expressed by the cell survival rate in temperature higher than a constant level for do a specific dose of the drug.[26] Many studies have demonstrated a relation between temperature dose and effect.[27] DFSs are higher if CEM43T90 (≥1 min). If such parameters have been achieved, the addition of HT effectively improves treatment outcomes. Such results were achieved in a Japanese study where temperature control parameters were among study priorities.[28] Similar results were achieved for breast cancer where better LC was only found in patients in whom higher temperatures were generated inside the tumour.[29] Harima and colleagues took note of a very high relevance of defining right temperature at each application of HT. In their reports, Harima has consistently analyzed, presented and implemented the treatment parameters. Certainly, those parameters include all the elements that affect HT in combination with RT and CT, such as increase in oxidation and perfusion during HT, importance of the duration of HT or the number of applications.[30,31]

3.1. *Evaluation of results of HT and RT*

The publication of a prospective multi-centre randomized study on the effects of HT added to radiotherapy (RT) in pelvic cancers in The Lancet, in 2000, marked a breakthrough in treatment results of LACC.[32] The method was regarded as particularly promising in the treatment of LACC. However, up to date, HT remains to be a controversial matter of debate.

In the aforementioned Dutch Deep Hyperthermia Trial (DDHT), a group of patients treated in 1990–1996 was characterized by large tumour >60 mm in diameter, i.e. highly locally advanced, performance status of World Health Organization (WHO) 0 or I, mean age 51 years, haemoglobin levels (Hgb) both < and >7 mmol/L. Remarkable overall survival (OS) results of 27% vs. 54%, improved local control (LC) from 41% to 61% at three-year follow-up of patients treated with hyperthermia added to radiotherapy were also confirmed at 12-year follow-up: OS of 20% vs. 37% and LC 37% vs. 56%, respectively (Table 1).[32,33] No statistically significant difference in toxicity was demonstrated between the HT and non-HT groups.[32,33]

The Dutch researchers also analyzed a group of patients from the following years. A group of 378 patients included in that study were at a worse condition according to the WHO scale (WHO 0–WHO III) and had larger tumours (mean diameter of 9 cm vs. 7.6 cm in DDHT). LC, which is the first condition for recovery and one of the primary endpoints in that study, was 53% after 5 years, thus confirming beneficial treatment results with HT added to RT. Five-year OS was 40% in the whole study group. Importantly, the treatment was found to cause no additional early or late toxicity that might arise from HT. In both studies, patients could have positive lymph nodes in diagnostic tests.[34]

Table 1 – Characteristics of the randomized control studies comparing RT and RT and HT since 2000.

Study and year	N	EBRT TD/fx Gy	BT TD fx Gy	FIGO Stage	Follow up (months)	CR RT	CR RT + HT	LC RT	LC RT + HT	OS RT	OS RT + HT
Harima 2001[35]	40	30.6 (WPRT) 52.2/1.8	30/7.5	IIIB	25(RT)/36(RT+HT)	50%	80%	49%*	80%* (SS)	48%*	58%* (NS)
Vasanthan 2005[36]	110	2–70/1.8–2.0	0–68/HDR (5–6) LDR (20–22)	IIB-IVA	~15.7	-	-	~70%*	~70* (NS)	~80%	~70% (NS)
Franckena 2008 (DDHT)[33]	114	40–50.4/1.8–2	17–18 (HDR) 20–0 (LDR)	IIB-IVA	108**	57%	83% (SS)	37%	61% (SS)	20%	37% (SS)

BT: brachytherapy; CR: complete response; DDHT: Dutch deep hyperthermia trial; EBRT: external beam radiotherapy; FIGO: International Federation of Gynacology and Obstetrics; fx: fraction dose; HT: hyperthermia; LC: local control; N, number; NS: not significant; OS: overall survival; RT: radiotherapy; SS: statistical significant; TD: total dose.

* At 3 years.

** For survivors.

Japan researchers reported the results from a study of 40 patients with LACC (only FIGO IIIB) treated with RT or RT+HT. They observed a difference in 3yrOS 48% for RT and 58% for RTHT, but it was not statistically significant.[35] However, they observed significant improvement in LC and complete response (CR) 50% and 49% for RT compared to 80% and 80% for RT+HT, respectively (Table 1). Toxicity was not significantly different between treatment groups.[35]

Vasanthan et al. from India reported the results from multicentre study in 110 patients with CC in stage FIGO IIB-IVA. No significant difference was observed both in LC and OS (Table 1). The quality of HT (partial intravaginal HT) described in this work was not sufficiently reported and explained.[35,36] The quality of HT probably played a major role and influenced the results of RT+HT in this trial.[37]

The position of HT as a method to greatly improve RT results in cervical cancer was further reinforced by the Cochrane Database analysis. It confirmed a complementary role of HT in combination with RT. RT supplemented with HT results in significantly statistically higher CR with relative risk of 0.56, lower local recurrence (LR) with Hazard Ratio (HR) of 0.48 and better OS with HR of 0.67. No additional toxicity was found. While many studies included in the analysis came from single centres, FIGO IIIB patients were in majority in each of them.[38]

3.2. *Evaluation of results of HT and RTCT*

For more than a decade, radiochemotherapy (RTCT) has been a standard procedure in LACC. That treatment modality is commonly accepted worldwide according to guidelines of many oncology societies, based on randomized study results that have illustrated its advantages as compared to radiotherapy alone.[3–7] Meta-analysis confirmed that treatment involving RTCT delivers better outcome than radiotherapy alone.[39] As the above studies differed from one another and a number of questions were raised as to their interpretation, another meta-analysis was performed to confirm that the improvement in five-year OS is 3% in patients with FIGO III–IVA and 7% in patients with IIB. At the same time, both reviews revealed a high growth of hematologic and gastrointestinal toxicity.[40]

The US studies received a wide coverage and, according to the National Cancer Institute guidelines, were implemented into clinical practice to change the existing course of action. Inclusion of cytotoxic agents into the standard management of cervical cancer requires the involvement of chemotherapeutic department, which are already there in every oncology centre, and does not require any additional equipment, infrastructure or investment.

However, considering the increased toxicity and still not fully satisfactory treatment outcomes, studies were initiated on a 'trimodality treatment'. Various mechanisms of action and toxicity profile encourage HT to be combined with both RT and simultaneous chemotherapy. A non-randomized prospective study including 69 patients from the US, Norway and the Netherlands treated with cisplatin-based RTCT administered weekly with HT applied once a week showed the safety of such a modality, and the 5-year treatment results were at least comparable to those achieved with a classic RTCT. Five-year relapse-free survival 57.5% (95% confidence interval (CI): 46.6–71.0) and five-year OS 66.1% (95%CI: 55.1–79.3).[41] To add a missing component of the above investigation, a Japanese group performed a randomized multi-centre clinical trial of RTCT + HT vs. RTCT alone. The trimodality was found to show a tendency towards better treatment outcomes, but without a statistically significant *p*-value. Again, that study did not demonstrate any increase in HT-induced toxicity. In the logistic regression analysis, the HT group achieved CR more often (88%) than the non-HT group (77.6%, Table 2).[28] However, as the authors indicate, the study inclusion criteria were quite restrictive. Patients with metastatic lymph nodes in the aorta region and haemoglobin level $\leq$10 g/dL were not included. Both factors are associated with a lower survival rate. This may also account for very good treatment outcomes in the RTCT arm. This should, consequently, lead to the change of initial statistical assumptions and a much larger group of subjects is needed to detect a statistically significant difference.[28]

In 2016, Lutgens et al. reported their results obtained in RADCHOC study (randomized control trial) including 87 patients with LACC. Median follow up was 7.1 years.[41] The study compared RTCT vs. RT+HT, but it was closed prematurely after enrolling 87 of the 376 planned patients. The results suggested comparable outcomes in terms of LC 78% vs. 80% and OS 69% vs. 69% at 5-years (Table 2). RADCHOC was designed to establish if radiotherapy combined with hyperthermia (RT+HT) should be preferred in bulky and/or FIGO-stage III. However, only 19% of patients in the RTCT and 24% in the RT+HT arm had tumours >6 cm.[42] RADCHOC trial did not provide an answer to the question if RTCT or RTHT should be preferred but it suggested that RT-HT provides an effective alternative radical treatment even for small tumours.[42]

A very important meta-analysis has recently been published in this subject matter. Data et al. on the comparison of RTHT vs. RT, RTCTHT vs. RT have been updated. A higher percentage of patients treated with RTHT and RTCTHT achieved CR and HTRT delivered higher OS as compared to RT alone (no such comparison was made for RTCTHT vs. RT). Grade III–IV acute toxicity and late complications were comparable.[43] Network meta-analysis was also used which, unlike classic meta-analysis, enables an indirect and direct analysis of more treatment methods. First, when comparing RTCT vs. RTCTHT, RT vs. RTCTHT, RT vs. RTCT, and RTHT vs. RTCTHT in the context of CR and OS, RTCTHT was found to be much more beneficial than RT and RTCT. Second, when comparing RTHT and RTCT with a network meta-analysis method, it was shown that CR RTHT performed better; however, in terms of OS both methods are comparable. The use of chemotherapy is associated with increased treatment toxicity, an effect that is not observed with HT.[43]

A particular case is that of HT combined with brachytherapy. Such treatment was carried out in Warsaw to check if interstitial brachytherapy (BT) combined with HT improves local control or disease free survival (DFS, Table 2).[44] The addition of HT was not observed to affect treatment outcomes. HT was only added to BT performed once a week following a completed stage of teleradiotherapy.[44] With HT used in that model, the high temperature's range of action is very limited, which causes the activity of HT to be limited, too. Further-

more the tumour is much smaller with fewer hypoxic foci. Previous studies have demonstrated the effectiveness of HT, particularly in primary tumours of large volume.

3.3. *Evaluation of results of HT and chemotherapy for recurrent or metastatic CC*

The outcome of treatment of recurrent or metastatic CC remains particularly poor. A probable reason for this is the decreased blood flow to the organs caused by vascular changes after RT. The most widely used drug is cisplatin alone or in combination with other drug topotecan or paclitaxel with response rate around 33%.[45,46] The addition of bevacizumab to chemotherapy increased OS (17 vs. 13 months) and resulted in higher response rates (48% vs. 36%). It was also associated with an increased toxitcity.[47]

The therapeutic potential of HT with chemotherapy in recurrent or metastatic CC was recognized at the end of last century. The results were confirmed by Richel et al. in 2004 in a phase II study. They observed 25 patients with recurrent or metastatic CC who had been treated with cisplatin monotherapy and whole body HT. CT+HT yielded very good treatment results i.e. CR ~5% and partial response (PR) ~28%, stable disease (SD) ~43%, 1yr OS ~36% (Table 3).[48] In addition, Franckena et al. presented more promising results in 2007 after the analysis of a group of 47 patients with recurrence or metastatic CC. The patients were treated with cisplatin and HT. They achieved 55% response rate (PR+CR) and 8 month median OS (Table 3).[49] On the other hand, the results presented seven years later by the same research group were completely different. Heijkoop et al. presented a group of 38 patients with recurrent or metastatic cervical cancer after RTCT with cisplatin. Median follow-up was 6.5 months.[50] The patients were treated with cisplatin and HT. Overall response rate (PR+CR) was 14% and 1 year OS was 23% (Table 3). The authors of the study do not recommend this treatment for recurrence of CC after RCTH.[50]

Recently, Lee et al. from South Korea have presented the results of treatment of patients with regional recurrence of CC. They administered chemotherapy with cisplatin, carboplatin, paclitaxel, 5-flurouracil and used modulated electro-hyperthermia in order to avoid the drawbacks of conventional electromagnetic heating.[51] The modulated electro-hyperthermia is designed to enhance the therapeutic response by heating selectively malignant tumours and tumour cells by modulated delivery of short radiofrequency waves of 13.56 MHz. This method of HT heats the malignant cell membrane, induces apoptotic cell death and promotes immunological response.[52–54] Median follow up was 11 months for the chemotherapy group and 13.5 months for chemotherapy with the HT group. The overall response rate (CR+PR+SD) was significantly higher in the group of patients who received chemotherapy and HT than in that who received chemotherapy alone: 72% vs. 40%, respectively.[51] The study has not shown any survival benefits between the groups (Table 3).

Table 2 – Characteristics of the randomized control studies comparing RTCH and HT.

Study and year	*N*	EBRT TD/fx Gy	BT (Gy)	FIGO	Follow up (months)	CT	CR RT	CR investigated arm	LC RTCT	LC investigated arm	OS RTCT	OS investigated arm
Zolciak-Siwinska 2013[44]	205	45–50/1.8–2.0 +10 boost LN+	30/7.5 HDR	II-III	45	CDDP 40 mg weekly	–	–	87%	RTCT+BT HT* 90% (NS)	70% 3yr DFS	RTCT+BT HT* 62% (NS) 3yr DFS
Lutgens 2016 RADCHOC[42]	84	50/2.0	21/7.0 HDR 29 MDR 32 LDR	IB2-IVA	85	CDDP 40 mg weekly	–	–	78%	RT+HT 80% (NS)	69%	RT+HT 69%(NS)
Harima 2016[28]	101	20–31.2/1.8–2.0 WPRT + 10–22 (Central)	20–30/5–6 HDR	IB-IVA	47–63	CDDP 30–40 mg weekly	77%	RTCT + HT 88%(SS)	60.6%	RTCT + HT 70.8% (NS)	71%	RTCT+HT 80% (NS)

BT: brachytherapy; CR: complete response; CT: chemotherapy; DFS: disease free survival; EBRT: external beam radiotherapy; FIGO: International Federation of Gynacology and Obstetrics; fx: fraction dose; HT: hyperthermia; LC: local control; *N*: number; NS: not significant; OS: overall survival; RT: radiotherapy; SS: statistical significant; TD: total dose; yr: years.

* Interstitial HT.

Table 3 – Characteristics of the studies of HT and CT as palliative approach in recurrent CC.

Study and year	Study type	N	Stage	Follow up (months)	Control arm	Investigated arm	Response rate incontrol arm	Response rate in investigated arm	Results control arm	Results investigated arm
Richel et al., 2004[48]	Phase II	21 (25)	Recurrent or metastatic CC	7.5 (OS)	CT (CDDP)+	Whole body	PD ~ 24% SD ~ 43% PR ~ 28% CR ~ 5%		1yrOS ~ 36%	1yrPFS ~ 16%
Franckena et al., 2007[48]	Phase I/II	47	Recurrent or metastatic ($n = 8$) CC after CT ($n = 12$), after HT ($n = 8$)	Median OS 8	CT (CDDP)+HT		PR +CR – 55%	Operability – 19% Palliation – 74%	Median OS 8 months	
Heijkoop et al., 2014[50]	Retrospective	38	Regional±local Recurrence of CC ± PALN+ after RTCT ± surgery (no pervious HT) 4 pts metastatic	6.5	CT (CDDP)+HT		PD – 51% SD – 35% PR – 11% CR – 3%		1yrOS – 23%	2yrOS – 4%
Lee et al., 2017[51]	Retrospective	38	Regional±local Recurrence of CC ± PALN+ after RTCT ± surgery (no pervious HT)	11 (CT), 13.5 (CT+HT)	CT (TP/TC/FP/CDDP) $n = 20$	CT – TP/TC/FP/CDDP + HT ($n = 18$) modulated electro-hyperthermia	PD – 60% SD – 5% PR – 15% CR – 20%	PD – 28% SD – 11% PR – 11% CR – 50% (SS)	~1yrOS 75%	~1yrOS 86%(SS)

CR: complete response; CT: chemotherapy; FP: cisplatin and 5-fluorouracil; HT: hyperthermia; N: number; NS: not significant; OS: overall survival; RT radiotherapy; SD: stable disease; PD: progressive disease; PR: partial response; SS: statistical significant; TC: paclitaxel and carboplatin; TP: paclitaxel and cisplatin; yr: years.

3.4. *State of the art and future perspectives*

As technology advances, HT enters a period of rapid development gaining more and more acceptance of the clinical community. The perception of HT in cancer treatment has been changed.

A very strong emphasis is put on the quality of HT used. Optimal treatment model for LACC still remains an open question. Despite so much evidence of efficacy and favourable outcomes without toxicity, HT is yet to be included in the NCCN recommendations for cervical cancer. It seems that now it is time to separate more specific groups of patients who could benefit the most from the addition of HT. Many factors need to be taken into account, as the disease responds to treatment in different ways depending on the stage. Prognosis for patients with metastatic lymph nodes of the aorta region (PALN+) is quite different from those with FIGO IB/IIA cancer. The HPV status, which has not been taken into consideration so far, is very important as it constitutes an independent prognostic factor. The main issue for investigators from centres having HT equipment is a poor recruitment of patients for studies. Another element to remember is the aforementioned diversity of HT equipment and quality of treatment delivered. Thermal parameters, length of application, frequency of use, intervals in combination with RT or CT are factors that affect effectiveness and, consequently, the results and outcomes.

Currently, two study projects recruiting LACC patients are open at ClinicalTrials.gov. One of them relates to the combination of HT with interstitial brachytherapy, and the other to cervical cancer spread beyond the pelvis in combination with HIPEC and chemotherapy. The third study is waiting for the recruitment to open for patients with cervical cancer but also diagnosed sarcoma of the extremities, in combination with MR-HIFU. When this article is being written, there is no registered open randomized trial concerning the combination of RTCT and HT, and RT and HT.

4. Conclusions

HT combined with other treatment modalities is part of a multidisciplinary oncological management in CC and should be more often used by the clinician. HT requires very reliable quality assurance. RT and HT is better than RT alone in primary treatment of LACC. In addition, RT and HT is a very good option for the primary treatment of LACC in patients with contraindications for RTCT due to a different toxicity profile. In the treatment of regional recurrence and metastatic CC after RTCT, HT with chemotherapy requires caution and further research.

Conflict of interest

None declared.

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