

# Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients

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## Abstract

**Introduction:** HIV infection is associated with increased treatment-related toxicity and worse outcomes in locally advanced cervical cancer patients (LACC), especially in resource-constrained settings. Local control (LC) in a phase III randomized, controlled trial investigating modulated electro-hyperthermia (mEHT) on LACC patients in South Africa (ethics registration: M120477/M190295), was significantly higher in participants randomized to receive chemoradiotherapy (CRT) with mEHT compared to CRT alone (stratum: HIV status, accounting for age and stage). This analysis investigates whether mEHT adds to the toxicity profile of CRT in HIV-positive LACC participants.

**Methods:** Inclusion criteria: signed informed consent; International Federation of Gynecology and Obstetrics stages IIB to IIIB squamous cell carcinoma of the cervix; HIV-positive patients: CD4 count >200 cell/ $\mu$ L/on antiretroviral treatment for >6 months; eligible for CRT with radical intent. Recruitment: January 2014 to November 2017 (ClinicalTrials.gov: NCT03332069). Acute toxicity (evaluated using CTCAE v4 criteria) and quality of life (according to EORTC forms) in 206 participants randomized for treatment were evaluated alongside the LC results to determine safety and efficacy in HIV-positive participants.

**Results:** Compliance to mEHT treatment was high (97% completed  $\geq$ 8 treatments) with no significant differences in CRT-related toxicity between treatment groups or between HIV-positive and -negative participants. Adverse events attributed to mEHT were minor, even in obese patients, and did not affect CRT compliance. Participants treated with mEHT reported improved fatigue, pain, emotional and cognitive functioning.

**Conclusion:** mEHT did not cause unexpected CRT-related toxicities and is a safe treatment modality for HIV-positive patients, with minor limitations regarding body weight, even in a low-resource setting.

**Keywords:** Modulated electro-hyperthermia, chemoradiotherapy, cervical cancer, early toxicity, quality of life, HIV

## Introduction

The incidence of locally advanced cervical cancer (LACC) in developed countries has decreased since the introduction of screening and Human Papilloma Virus (HPV) vaccination programs [1,2], yet morbidity and mortality rates remain high in low-resource settings [3]. Radiotherapy (RT) with weekly concurrent cisplatin is the standard of care for LACC [4], however in patients who are unable to receive cisplatin, hyperthermia (HT) delivered at 40–43 °C for 60–90 min has shown to be as effective as a radiosensitizer [5]. Studies have shown that HT plus RT improves local disease control (LDC) and survival in LACC patients, compared to RT alone, without significant effects on RT-related toxicity [6–10]. Hyperthermia has been investigated as a chemo-sensitizer with response rates of more than 50% and acceptable toxicity for the management of recurrent or residual cervical tumors [11,12] and phase II studies have demonstrated the safety of the addition of HT to chemoradiotherapy (CRT) [13–15]. Adverse events directly attributed to HT include pain (8%), superficial burns (6–18%) [10,13], subcutaneous fatty burns (8–12%) [5,10,11,13], and infections after the introduction of interstitial thermometry catheters [10]. A retrospective analysis of 420 patients treated with RT and HT reported that 153(36%) participants developed subcutaneous tissue toxicity, ranging from grade 1–3 in severity, with one patient requiring surgical intervention [16]. Acute neurotoxicity following the treatment of deep pelvic tumors with HT is a rare (2.3% incidence) complication which can have an impact on the daily activities of the patient [5,17].

The effect of HIV infection on the treatment of LACC patients includes increased multi-system RT-related toxicity, treatment interruptions, higher risks of residual disease [18] and lower survival rates [19]. Increased chromosomal radio sensitivity has been observed in the lymphocytes of HIV-positive

patients, compared to HIV-negative patients [20,21]. Fibroblasts from the skin of HIV-positive Kaposi Sarcoma patients are more sensitive to ionizing radiation (IR) when compared to those of healthy controls [22] and extreme mucositis has been reported in HIV-positive patients [23]. Housri et al. [24] recommend that HIV-positive patients treated to the head and neck, abdomen and pelvis, with RT, should be closely monitored for possible mucosal reactions and HIV-positive patients treated with CRT should be closely monitored for hematologic toxicity. Possible contributors to the increased radio sensitivity of HIV-positive patients include a systemic glutathione deficiency caused by HIV infection, resulting in the depletion of radio-protective thiols and increased oxidative stress [25], and the effect of the HIV-1 Tat protein on the cellular capacity of certain cells to repair radiation-induced DNA double strand breaks [24]. Information on the use of modulated electro-hyperthermia (mEHT) as a radiosensitizer in HIV-positive patients, who may be more likely to experience RT-related toxicity, is not available and therefore requires investigation.

## **mEHT**

mEHT is a capacitive technology which transmits amplitude modulated radiofrequency (RF) waves at a frequency of 13.56 MHz, between two electrodes [26–29]. The small electrode is covered by a water bolus in an adjustable arm, and the large electrode is in the bed and is covered by a water mattress. The amplitude modulation, which is the main difference between mEHT and other capacitive devices, is described elsewhere in the literature and is purported to be a key component of the enhanced efficiency of mEHT, allowing for a lower power output [29,30]. The effects of the amplitude modulation are not yet fully understood and are still under debate.

Preclinical studies have shown that mEHT is distinctly more effective than water-bath, infrared, or RF-hyperthermia, if adjusted to the same temperature [31] and mEHT, when applied at 42 °C, induces both thermal and non-thermal effects on cells. In a study by Andocs et al. [32], the ratio of cell killing was enhanced by a factor of 3.2 in tumors treated with mEHT at 42 °C in comparison to tumors treated with infrared heating at 42 °C, reflecting the non-thermal effects of mEHT and the potentiation of the effects of radiofrequency heating at 13.56 MHz by the addition of amplitude modulation.

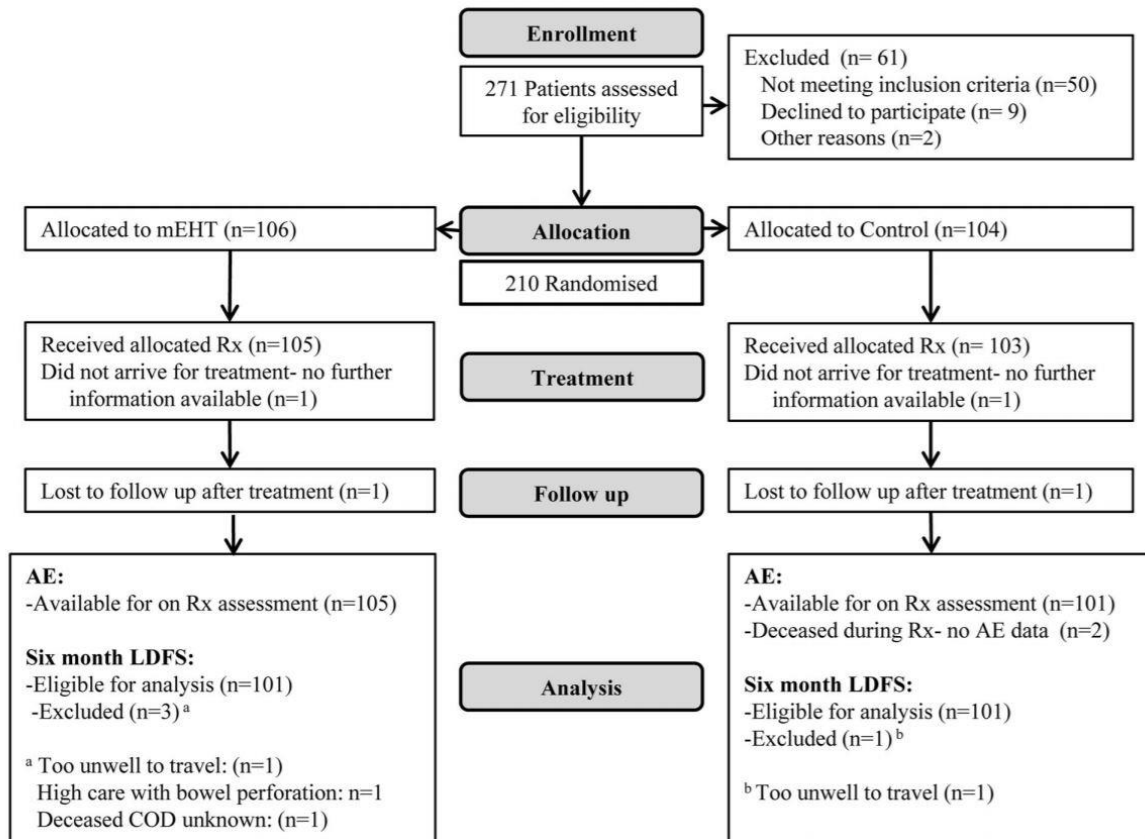
Lee et al. [33] observed an increase in temperature to a maximum average of 38.5 °C in cervical tumors after 60 min heating at a planned power output 150 W (although the actual power output is not described in the article), which is 20 W higher than our planned maximum power output. This was accompanied by an increase in blood perfusion. The same group showed that mEHT combined with platinum-based chemotherapy improved outcomes for recurrent/residual disease in cervical cancer patients [34]. The mild temperatures reached during mEHT treatments alone cannot explain the improved outcomes seen after the mEHT treatments, confirming the importance of the addition of amplitude-modulation. The specific interaction of mEHT in tumors allows for an effective treatment with less total power in comparison to conventional RF-systems. The data reported in the studies by Lee et al. [33,34] provided the rationale to evaluate the use of mEHT for the primary management of locally advanced and nonresectable cervical cancer.

mEHT is being investigated in a phase III randomized controlled trial as a radiosensitizer (whole pelvic radiation), combined with cisplatin, for the treatment of LACC in a low-resource setting and in HIV-positive and -negative patients. This is the first randomized controlled trial on mEHT combined with CRT for LACC, and the only study in a low-resource setting and in HIV-positive patients. Table 1 summarizes the local control (LC) outcomes at six months post-treatment, as reported by Minnaar et al. [35]. Two hundred and two participants were eligible for LC analysis (mEHT: n = 101; Control: n = 101) at 6 months post-treatment, of which 171 (mEHT: n = 88 (87.1%); Control: n = 83 (82.2%)), were alive at six months post-treatment. The study did not show any significant difference in treatment related toxicity between the two treatment groups [35].

**Table 1.** Summary of local control outcomes at 6 months post-treatment in the trial by Minnaar et al. [35].

	mEHT group	Control group	p-value
Tumor response on PET/CT	49/85 (58%)	26/73 (36%)	0.005
LC censored for survival	40/88 (45%)	20/83 (24%)	0.003
LDFS	39/101 (39%)	20/101 (20%)	0.003

PET/CT: position emission tomography/computed tomography; LC: local control; LDFS: local disease free survival.



*Figure 1. CONSORT diagram of the 271 patients who were screened and subsequently included or excluded in the trial, as reported by Minnaar et al. [35] and available for evaluation of early toxicity. AE: adverse events; COD: cause of death; LDFS: local disease free survival; Rx: treatment.*

Participants who were eligible for evaluation of LC by 18Fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) scans (creatinine clearance >60 ml/min, controlled glucose levels, were able to lie still for the duration of the scan), had a second 18F-FDG PET/CT scan at six months post-treatment. Local control was considered a failure if any disease was confirmed either by 18F-FDG PET/CT, CT, clinical examination, cytological evaluation or fine needle aspiration of palpable lymph nodes in the radiation field. Participants treated with mEHT were significantly more likely to achieve six-month local disease-free survival (LDFS; odd ratio (OR): 0.36, 95% confidence interval (CI): 0.19–0.69;  $p = 0.002$ ) and the association between HIV status and six month LDFS was not significant ( $p = 0.338$ ). The authors reported that the age, number of cisplatin doses, treatment time, RT dose, and CD4 count, were not significant predictors of six-month LDFS. In the mEHT group, body mass index (BMI), number of mEHT treatments, and energy dose were not predictors of six-month LDFS. In a preliminary report on the first 70 participants in the study to reach two years post-treatment, two year survival was more likely in the participants treated with mEHT

(78 vs. 65%; Prob>  $\chi^2 = 0.0334$ ; adjusted for age), as was 2-year progression free survival, adjusted for age (76 vs. 61%; Prob>  $\chi^2 = 0.0317$ ) [36].

In order to determine the effects of mEHT on CRT-related toxicity in HIV-positive participants, an analysis of the acute toxicity and quality of life of HIV-positive versus HIV-negative participants in the study by Minnaar et al. [35,36] was conducted. The effects of characteristics such as obesity on the frequency of adverse events in the study sample are included in this report. Quality of life (QoL) characteristics, such as physical well-being, can have an impact on clinical outcomes [37] and given the high morbidity associated with LACC, CRT treatment and with HIV-infection, QoL in the HIV-positive and HIV-negative participants in each treatment group is also reported.

## **Materials and methods**

An ongoing phase III randomized controlled trial is being conducted at the Charlotte Maxeke Johannesburg Academic Hospital in Gauteng, South Africa, by the Radiation Sciences Department at the University of the Witwatersrand. The sample size calculation was based on the estimated required sample sizes for a two-sample comparison of survivor's functions at two years with a minimum sample size of 200 participants. A total of 271 patients were screened between January 2014 and November 2017, of which 210 were randomized for trial (see Figure 1). A stratified on-line software generated random-sampling tool supplied by the data management system, REDCap, was used to randomize participants to either the Control or mEHT Group; stratum: HIV status. Randomization accounted for age (<30 years; 30–50 years; >50 years), and International Federation of Gynecology and Obstetrics (FIGO) stage (IIB; IIIA and IIIB). The outcomes are the local disease control at six months post-treatment (reported by Minnaar et al. [35]) and 2-year survival. Approval has been obtained to follow participants for 5 years post-treatment. The 2- and 5-year follow-up period is ongoing and is expected to be completed in 2023. This analysis includes the 206 participants who arrived for treatment after randomization (mEHT Group: n = 105; Control Group: n = 101). Eligibility for the trial, as well as randomization and masking, are described previously [35].

### ***Compliance with ethical standards***

All procedures performed and work conducted in this trial involving human participants was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190295/M120477). The trial was registered on ClinicalTrials.Gov (ID: NCT03332069), and, as required by the institutional research committee, on the National Clinical Trials Register of South Africa (ID: 3012) before recruitment began.

### ***Informed consent***

All participants in the clinical trial described in this article have given written consent: to the inclusion of material pertaining to themselves; that they acknowledge that they cannot be identified via the article and that they have been fully anonymized in the report. The written consent obtained from all participants was approved by the institutional Human Research and Ethics Committee.

### ***Treatment***

All participants were planned to receive 50 Gy external beam radiation (EBRT) in 25 fractions, 24 Gy high dose rate (HDR) brachytherapy (BT) in three fractions (36 Gy equivalent dose in 2 Gy fractions

for an alpha-beta ratio of 10; source used: Iridium-192), and two doses of cisplatin (80 mg/m<sup>2</sup>) 21 days apart, not on mEHT or HDR BT days (subject to the participant's ability to receive cisplatin), as per institutional protocol. The EBRT target volume was planned and delivered to the whole pelvis using a four-field box technique on one of four Siemens linear accelerators in the department.

Two mEHT (Model: EHY2000+; Manufacturer: Oncotherm GmbH, Troisdorf, Germany) treatments were administered per week (maximum 10). mEHT was applied immediately before external beam radiation with a maximum of 30 min between the completion of mEHT and the completion of EBRT. This protocol was based on logistics and work-flow integration in the public hospital. A 30 cm electrode was used in the adjustable arm in order to cover as much of the pelvic field as possible. The treatment power was started at 60 W and increased using a step-up protocol over five minutes to the desired power of 90 W for the first treatment, 105 W for the second treatment, and a planned 130 W for the third and subsequent treatments (See Supplementary 1: hyperthermia schedule). Treatments were planned for a minimum of 55 min and a minimum energy dose of 360KJ per treatment. The first treatment is a safety treatment during which the participant is acclimatized to the treatment and the operator was able to identify potential risks. The first treatment is therefore administered at a low power without modulation.

### **Thermometry**

It is recommended that thermometry be used to evaluate the efficiency of hyperthermia treatments [38,39], however this is associated with challenges such as increased cost and complexity, and the ability to heat uniformly and consistently regardless of tumor and patient characteristics [40]. Within the mEHT concept non-thermal (energy-dependent) effects are supposed to provide the dominant sensitization effect. As the temperature increase is limited and the temperature is not considered a key parameter in this concept, there is no need to measure it. Instead the applied dose of mEHT was controlled by measurement of the energy, which can be measured more easily and reliably [26,28,41]. This principle makes administering the treatments less complex and less costly and suggests that mEHT could be suitable for low-resource settings.

### **Outcome measures**

Adverse events that occurred within 90 days of the start of RT were considered acute RT-related toxicity. The study utilized the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 from the National Cancer Institute (NCI) to define adverse events. The toxicity data was tabulated by treatment arm and HIV status. Thirty-nine adverse events from six categories (upper gastrointestinal (GIT); lower GIT; genitourinary tract (GUT); dermatologic and subcutaneous; neurological; hematological) at three time points (on treatment, six weeks and three months post-treatment) were analyzed. The frequency of all toxicities was reported and separate analyses for grade 3–4 toxicities for each system were conducted. Ototoxicity and peripheral neuropathy were grouped together under neurological toxicities, as these are both known to be potential cisplatin-related toxicities [42–44]. Adipose tissue burns, presenting as hard, painful, mobile masses within the adipose tissue, were classified according to the CTCAE v4.0 criteria under the heading 'Skin and subcutaneous tissue disorders—Other'.

QoL was measured at enrollment and again at six weeks, and three months post completion of treatment using the validated quality of life questionnaires (QLQ) C30 and Cx24, from the European Organization for Research and Treatment of Cancer (EORTC). Validated translations were available in English, Afrikaans, isiZulu, Sesotho, and isiXhosa [45]. The QLQ-C30 incorporates five functional

scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status, and perceived financial impact of the disease [46]. The QLQ Cx24 contains symptoms specific to cervical cancer and its treatment [47]. For the literate participants, the QLQ forms were provided in five different languages and the participants completed the forms themselves. For illiterate participants, nurses were asked to administer the forms and translate as needed. Nurses were blinded to the treatment group into which the participants were randomized. All scoring and reporting were done in accordance with the manual published by the EORTC which is made available with the QLQ forms.

### **Statistics**

Chi-squared tests were employed to assess observed frequency differences of all toxicities in each treatment arm and by HIV status. Multivariate logistic regression models were used to determine predictors of outcomes such as the development of grades 3–4 toxicity.

For QoL, items were scored and analyzed according the EORTC scoring manual and were linearly converted to scores from 0–100 where a high score represents higher functioning or a higher symptom experience [48]. Unpaired t-tests were used to analyze differences in linear scores between the groups at each event. Paired t-tests were used to evaluate the changes in the linear scores between the groups.

Two-sided p-values are reported and p values <0.05 were considered significant. STATA 13.0 Statistics software program (Stata Corporation, College Station, TX), was used to analyze the data.

### **Role of the funding sources**

The funding sources did not have any role in protocol design, data collection, analysis or reporting. The corresponding author had full access to all the data and was responsible for the final submission.

### **Results**

The median age was 48.7 (range: 26.5–72.2 years), 63.6% of participants had stage III disease and 51% of participants were HIV-positive. Patient and treatment characteristics were evenly matched in both treatment groups as listed in Table 2.

### **Radiotherapy**

The median time to complete RT was 41 days in both treatment groups with a range of 13–65 days in the mEHT group and 10–97 days in the control group. Reasons for taking in excess of 51 days to complete all RT include skin desquamation, bleeding and anemia, vomiting and dehydration and technical causes (such as machine services and repairs). The frequency of RT delays was significantly associated with HIV status ( $\chi^2$ :  $p = 0.020$ ) with 12(11.4%) delays in the HIV-positive participants versus three (3%) delays in the HIV-negative participants (OR: 0.237;  $p = 0.030$ ; 95% CI: 0.065–0.868). The association between treatment arm and RT delays was not significant with six out of 105(5.7%) in the mEHT group versus nine out of 101(8.9%) in the control group ( $\chi^2$ :  $p = 0.377$ ; OR: 1.614;  $p = 0.381$ ; 95% CI: 0.553–4.712).

**Table 2.** Characteristics of participants and treatment.

	mEHT 105	Control 101	<i>p</i> -value
HIV status			
Positive	52 (50%)	53 (53%)	
Negative	53 (50%)	48 (48%)	
FIGO staging			
IIB	40 (38%)	35 (35%)	
III	65 (62%)	66 (65%)	
Race			
African	97 (92%)	94 (93%)	
Caucasian	4 (4%)	1 (1%)	
Other	4 (4%)	6 (6%)	
Age (years)			
Mean	48.1	49.4	0.384
SD	10.8	10.3	
Range	26.5–68.9	28.4–72.7	
BMI			
Mean	27.8	27	0.387
SD	6.92	6.48	
Range	15–49	15–42	
Total RT dose			
Mean	84.7Gy	85.3	0.483
SD	7.61Gy	5.69	
Range	20Gy–86Gy	30–86Gy	
Treatment days			
Mean	41.6	42.8	0.255
SD	5.96	8.81	
Range	13–65	10–97	
Number of cisplatin doses			
Mean	1.37	1.28	0.323
SD	0.67	0.69	
0 doses	11 (11%)	14 (14%)	
1 dose	44 (42%)	45 (45%)	
2 doses	50 (48%)	42 (42%)	
CD4 count (cells/ $\mu$ L)			
Mean	586.1	525.1	0.242
SD	258.6	272.8	
Range	148–1204	95–1524	
No of mEHT doses			
Mean	9.26		
SD	1.65		
Range	1–10		
Average KJ administered during mEHT			
Mean	380.18		
SD	32.07		
Range	237.1–454.5		

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics; KJ: kilojoules; RT: radiation therapy; SD: standard deviation.

**Table 3.** Reasons for missed or delayed cisplatin.

	One dose		No cisplatin	
	mEHT	Control	mEHT	Control
Renal dysfunction	19	11	7	10
Delayed first dose <sup>a</sup>	10	7		
Leucopenia	0	0		
Noncompliant	2	0	1	1
Anemia	1	2	2	1
Missed dose	1	1		
Vomiting dehydration	1	0		
Deceased	1	1		
Sepsis	0	3		
Technical	0	3		
Too weak	0	1	0	1
Dehydration	0	1		
Low CD4 count			0	1
Total	35	30	10	14

<sup>a</sup>Reasons for delayed first dose were renal dysfunction (mEHT: *n* = 1; Control: *n* = 1), leucopenia (mEHT: *n* = 2; Control: *n* = 1), non-compliant (mEHT: *n* = 0; Control: *n* = 1), anemia (mEHT: *n* = 4; Control: *n* = 4), sepsis (mEHT: *n* = 2; Control: *n* = 1) and supply problems (mEHT: *n* = 1; Control: *n* = 0).



## **Cisplatin**

Ten (9.5%) and 14 (13.9%) of mEHT and control group participants, respectively did not receive cisplatin. The mEHT group received a mean of 1.37 cycles and the control group received a mean of 1.28 cycles ( $p = 0.323$ ) of cisplatin. The most common reasons for omission of the second cycle were renal dysfunction (mEHT:  $n = 19$ ; Control:  $n = 11$ ), followed by a delay in the administration of the first cycle (mEHT:  $n = 10$ ; Control:  $n = 7$ ). Table 3 lists the reasons for cancellation/omission of cisplatin.

In  $\chi^2$  analyses, there were no significant associations between HIV status and number of cisplatin cycles ( $p = 0.549$ ) or delays ( $p = 0.444$ ) or between treatment arm and number of cisplatin cycles ( $p = 0.610$ ) or delays ( $p = 0.575$ ). HIV status was not a predictor of cisplatin dose delays (OR: 0.795;  $p = 0.452$ ; 95%CI: 0.436–1.448), or cancellations (OR: 0.735;  $p = 0.474$ ; 95%CI: 0.316–1.709). Likewise, the treatment group was not a predictor of cisplatin dose delays (OR: 1.180;  $p = 0.588$ ; 95%CI: 0.648–2.150), or cancellations (OR: 1.504;  $p = 0.348$ ; 95%CI: 0.641–3.530).

## **mEHT-specific toxicity**

One hundred and five participants were treated with mEHT of which 102 (97%) were able to receive eight or more ( $\geq 80\%$ ) of the mEHT treatments. One participant had four treatments and two participants had six treatments. Of the three participants who received less than eight mEHT treatments, two had a Body Mass Index (BMI) over 25 and all three reported adipose burns, which was the cause for the reduction in the number of mEHT treatments.

Of the 105 participants treated with mEHT, 17(16.2%) reported adverse events: grade 1–2 adipose tissue burns ( $n = 10$ , 9.5%); grade 1 surface burns ( $n = 2$ , 2.0%) and pain ( $n = 9$ , 8.6%). Four (23.5%) of the participants with adverse events had a normal BMI and 13(76.5%) were overweight (BMI 25–29.9) or obese (BMI  $>30$ ) [49]. A multivariate analysis showed that HIV status (OR: 1.47;  $p = 0.500$ ; 95% CI: 0.480–4.512), increased BMI (OR: 1.78;  $p = 0.375$ ; 95% CI: 0.499–6.335) and average energy (in Kilojoules) administered (OR: 0.986;  $p = 0.067$ ; 95% CI: 0.98–1.00) were not significant predictors of adverse events associated with mEHT treatments.

A significant difference in grade 1–2 adipose burns between the treatment groups in the on-treatment analysis (mEHT: 10 out of 105(9.5%) compared to Control: 1 out of 101(1%);  $p = 0.023$ ) was noted. This difference was not significant at six weeks or three months post-treatment.

## **Early toxicity analyzed by treatment group**

The toxicities were analyzed by treatment group in order to determine if the addition of mEHT had any effect on the toxicity of either the chemotherapy or radiotherapy. Chi-squared frequency tables showed a significant association between the number of grade 1–2 neurological toxicities and the addition of mEHT (mEHT Group:  $n = 5$ (5%); control group:  $n = 0$ (0%);  $p = 0.030$ ) at three months post treatment. The neurological toxicities reported were tinnitus ( $n = 1$ ; HIV-positive), hearing loss ( $n = 2$ ; one HIV-negative and one HIV-positive participant) and peripheral neuropathy ( $n = 3$ ; all in HIV-negative participants). However, the significance of the association between treatment group and toxicity disappeared when the neurological toxicities were separated into peripheral neuropathy ( $p = 0.095$ ) and ototoxicity ( $p = 0.174$ ). Only one participant developed grade 3–4 neurological toxicity (HIV-positive, in the mEHT group, treated with cisplatin). There were no other significant associations between the treatment group and grade 1–2 or grade 3–4 toxicities. Supplementary 2 contains the results of the Chi-squared analyses comparing the grades 3–4 toxicities of each treatment group, and the grades 3–4 toxicities reported by HIV-positive compared to the HIV-negative participants.

### Early toxicity analyzed by HIV status

There were some significant differences in specific symptoms associated with HIV status (diarrhea; creatinine clearance; vomiting and pigmentation); however, no clear pattern of association between the significant toxicities and mEHT treatments could be seen. At six weeks post treatment, HIV-negative participants reported a significantly higher frequency of grade 1–2 upper GIT symptoms, including nausea and vomiting (HIV-positive:  $n = 0(0\%)$ ; HIV-negative:  $n = 4(4\%)$ ;  $p = 0.044$ ). No other significant associations were seen in our sample (see Supplementary 2).

Participants were then further analyzed by HIV status within each treatment group in order to identify any effect of mEHT on toxicity in HIV-positive participants. These results are shown in Table 4. In the mEHT Group, there were more grade 3–4 renal toxicities in the HIV-positive participants ( $n = 5$ ) than in the HIV-negative participants ( $n = 0$ ) on treatment ( $p = 0.027$ ). In comparison, the control group had three HIV-positive (6%) and three HIV-negative participants (6%) who developed grade 3–4 renal toxicity ( $p = 0.900$ ). Eight of the participants with grade 3–4 renal toxicities were HIV-positive and three were HIV-negative ( $p = 0.137$ ) and the difference by treatment group overall was not significant (mEHT:  $n = 5(5\%)$ ; Control:  $n = 6(6.3\%)$ ;  $p = 0.707$ ). In the control group there were significantly more grade 1–2 lower GIT toxicities on treatment reported in the HIV-positive participants ( $n = 28(53\%)$ ) vs.  $n = 15(31\%)$ ;  $p = 0.028$ ). However, at six weeks post-treatment there were significantly more grade 1–2 upper GIT toxicities in the HIV-negative control group participants than in the HIV-positive control group participants ( $n = 0(0\%)$  vs.  $n = 4(8\%)$ ;  $p = 0.043$ ).

**Table 4.** Frequency of grade 3–4 toxicities in each treatment group analyzed by HIV status.

	mEHT			Control		
	HIV-positive	HIV-negative	<i>p</i> -value	HIV-positive	HIV-negative	<i>p</i> -value
<b>On treatment</b>	<i>n</i> = 52	<i>n</i> = 53		<i>n</i> = 53	<i>n</i> = 48	
Hematologic	6 (12%)	6 (11%)	0.972	8 (15%)	6 (13%)	0.706
Neurological	1 (2%)	0 (0%)	0.310	0 (0%)	0 (0%)	
Lower GIT	0 (0%)	1 (2%)	0.320	0 (0%)	0 (0%)	
Upper GIT	0 (0%)	1 (2%)	0.320	0 (0%)	0 (0%)	
Dermatologic	3 (6%)	1 (2%)	0.299	1 (2%)	1 (2%)	0.727
Urogenital	3 (6%)	1 (2%)	0.299	1 (2%)	2 (4%)	0.500
Renal	5 (10%)	0 (0%)	0.027*	3 (6%)	3 (6%)	0.900
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
<b>Six weeks</b>	<i>n</i> = 48	<i>n</i> = 50		<i>n</i> = 48	<i>n</i> = 47	
Hematologic	0 (0%)	2 (4%)	0.162	3 (6%)	3 (6%)	0.979
Neurological	1 (2%)	0 (0%)	0.305	0 (0%)	0 (0%)	
Lower GIT	1 (2%)	0 (0%)	0.490	0 (0%)	0 (0%)	
Upper GIT	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Dermatologic	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0.320	
Urogenital	1 (2%)	0 (0%)	0.305	0 (0%)	2 (4%)	0.149
Renal	1 (2%)	0 (0%)	0.490	0 (0%)	0 (0%)	
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
<b>Three months</b>	<i>n</i> = 45	<i>n</i> = 48		<i>n</i> = 43	<i>n</i> = 42	
Hematologic	3 (7%)	0 (0%)	0.069	1 (2%)	5 (12%)	0.085
Neurological	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Lower GIT	0 (0%)	1 (2%)	0.330	1 (2%)	2 (5%)	0.543
Upper GIT	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0.320	
Dermatologic	1 (2%)	0 (0%)	0.299	0 (0%)	0 (0%)	
Urogenital	1 (2%)	0 (0%)	0.299	1 (2%)	3 (7%)	0.294
Renal	3 (7%)	0 (0%)	0.069	1 (2%)	2 (5%)	0.543
Multiple	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

GIT: gastrointestinal tract.

\*Significant.

## Multivariate regression analyses

In a multivariate regression analysis for the development of early toxicities in each system, HIV status, the number of cisplatin doses, and the treatment group, were tested for predictors of outcomes. These results are shown in Table 5. Seven participants developed grade 1–2 neurological toxicities, six of which were in the mEHT group, and the only participant to develop grade 3–4 neurological toxicities was also in the mEHT group. The odds of developing a neurological toxicity were therefore almost eight times higher in patients treated with mEHT (OR: 7.98;  $p = 0.053$ ; 95%CI: 0.98–65.19). However, this was not a significant predictor of neurological toxicity development in the multivariate regression analysis, but cisplatin was a perfect predictor of the development of neurotoxicity, with all participants reporting neurotoxicity having received cisplatin. HIV-infection and receiving cisplatin were both significant predictors of the development of dermatological or subcutaneous early toxicities. Cisplatin was a significant predictor of renal toxicity (OR: 0.13;  $p < 0.005$ ; 95% CI: 0.05–0.33) while HIV-status and the administration of mEHT were not significant predictors of renal toxicity.

**Table 5.** Regression analysis for overall acute toxicity by system.

Variable	Odds ratio [OR]	<i>p</i> -value	95% CI
<b>Neurological</b>			
HIV status	0.82	0.771	0.21–3.20
Cisplatin	All participants with neurological adverse events received cisplatin		
mEHT	7.98	0.053	0.98–65.19
<b>Dermatologic/subcutaneous</b>			
HIV status	2.61	0.033*	1.08–6.29
Cisplatin	3.54	0.016*	1.27–9.84
mEHT	1.35	0.485	0.58–3.11
<b>Renal</b>			
HIV status	0.58	0.098	0.30–1.12
Cisplatin	0.13	<0.005*	0.05–0.33
mEHT	0.95	0.887	0.50–1.82

\*Significant.

## Quality of life

There were no statistically significant differences in QLQ scores between the two groups at baseline assessment. At the 6-week time point the mean change in cognitive function in the mEHT group was significantly higher than in the control group. At three months post treatment, fatigue and pain were significantly reduced in the mEHT group (Table 6).

**Table 6.** Significant changes in the QoL results.

	mEHT group			Control group			<i>p</i> -value
	Mean change	SD	95% CI	Mean change	SD	95% CI	
Six weeks							
Cognitive function	13.6	33.1	6.97–20.24	3.5	30.6	2.89–9.85	0.031
Three months							
Social functioning	83.9	31.6	77.4–90.4	73.3	39.4	64.8–81.8	0.049
Emotional functioning	83.9	24.3	78.9–88.9	73.5	33.3	66.3–80.6	0.017
Fatigue	–13.6	26.0	–18.86 to –8.15	3.0	39.9	11.53–5.59	0.037
Pain	–21.0	33.0	27.76 to –14.18	–6.7	36.6	–14.62 to 1.05	0.007

SD: standard deviation.

At the three month time point there was an overall improvement in the mEHT group with significant improvements in: social functioning (mEHT: mean: 83.9, SD: 31.6, 95%CI: 77.4–90.4; Control: mean:

73.3, SD: 39.4, 95%CI: 64.8–81.8;  $p = 0.049$ ), and emotional functioning (mEHT: mean: 83.9, SD: 24.3, 95%CI: 78.9–88.9; Control: mean: 73.5, SD: 33.3, 95%CI: 66.3–80.6;  $p = 0.017$ ). The mean improvement in social, emotional and physical function at six weeks post-treatment was significantly higher ( $p = 0.0048$ ; 0.0141 and 0.0155, respectively) in participants who had a complete response. Social-and emotional function continued to be higher in participants with a complete response at six months post-treatment ( $p = 0.0074$  and 0.0035, respectively), as was the perception of body image ( $p = 0.0496$ ). Supplementary 3 tabulates the significant improvements in QoL alongside the local control at six months post treatment.

## Discussion

Models have shown that RF capacitive heating to deep pelvic tumors is not possible without severe adipose burns [50,51]. mEHT is a capacitive technology which has shown to increase the effectiveness of CRT in the management of LACC patients [35] despite the surprisingly low power output compared to other capacitive technologies. The cell killing effects of ionizing radiation are enhanced with the addition of mEHT at 41 °C to RT treatment regimens, as shown in preclinical [52] and clinical studies [35], and mEHT has shown to be cytotoxic at temperatures of only 38.5 °C [32,53]. Temperatures above 40 °C are not required during mEHT treatments as the dominant effect is non-thermal [32], allowing for a lower power output and for the treatment of deep seated cervical tumors [34,35], even in participants with a BMI of >27, with extremely low toxicity. These non-thermal effects are a result of the amplitude modulation.

In a theoretical model by Wust et al. [54], the temperature increase in the tumor during mEHT was not relevant and in clinical practice Lee et al. [33] demonstrated only mild temperature increases in cervical tumors treated with mEHT. The improved outcomes observed with the addition of mEHT to treatment protocols for cervical cancer [34,35] despite the low temperatures, corroborate the hypothesis that the dominant effects of mEHT may be non-thermal [32].

Although subcutaneous burns (grade 1–2) due to mEHT were significantly higher in the mEHT Group on treatment, these resolved by three months post-treatment and the overall dermatological and subcutaneous toxicity was not significantly different between the treatment groups. Subcutaneous adipose tissue is particularly sensitive to the effects of EBRT and exposure to radiation can lead to an alteration of the tissue's developmental potential [55] and fibrosis of the soft tissues is a known complication of EBRT [56]. It is therefore not unexpected that one participant in the control group presented with what appeared to be a subcutaneous burn at six weeks post-treatment. Our participants reported less subcutaneous toxicity than other studies using HT techniques in which a much higher power is applied. Additional thermometry to measure the skin temperature and prevent burns is therefore not necessary during mEHT, likely due to the effective cooling mechanisms and lower power output.

The development of neurotoxicity was more frequent in the mEHT Group however cisplatin was a perfect predictor of neurotoxicity in the multivariate regression analysis and was therefore the most likely cause of the development of neurotoxicity. Although peripheral neuropathy is a known but rare side effect of HT to the pelvis [5,17] and we therefore cannot exclude the potential effects of deep heating on the development of peripheral neuropathy related to increased local effectiveness.

In our participants treated with mEHT, the adverse events were less frequent and less severe than what is expected based on available literature [5,10,11,13,16,57], our participants could receive more

treatments (allowing for up to two treatments per week with a total of ten treatments), and the local control outcomes were significantly improved [35].

## **HIV**

In our study, HIV infection was associated with an increased rate of RT delays; however, it was not a predictor of RT-related toxicities as reported in the literature [19,58,59]. The increased rate of renal toxicity in HIV-positive participants treated with mEHT, and decreased rate of renal toxicity in HIV-negative participants treated with mEHT, compared to the control group, is an unexpected result. Although the multivariate analysis showed cisplatin to be a significant predictor of renal toxicity, while HIV-status and treatment group were not significant predictors of renal toxicity, we suggest that renal function be closely monitored in HIV-positive patients treated with mEHT to the pelvis, combined with CRT.

All of our participants had either been on antiretroviral therapy (ART) for longer than six months or had a CD4 count above 200 cells/ $\mu$ L and this may have contributed to the improved outcomes and lower hematological toxicities seen in our HIV-positive participants, compared to reports in the literature. We did not observe significant differences in CRT or mEHT-related toxicity between HIV-positive and -negative patients, indicating that mEHT can be safely applied with CRT in HIV-positive patients. We did however observe an increase in upper GIT symptoms, such as vomiting, in the HIV-negative participants, which was also seen in a study analyzing the differences in CRT-related toxicities in HIV-positive (on ART; CD4 count  $>200$  cells/ $\mu$ L) and HIV-negative cervical cancer patients in Zambia [60].

## **Temperature and thermometry**

Thermometry in this study was not carried out as recommended with standard RF-capacitive heating or phased array heating techniques [61,62]. Thermometry is applied during HT treatments in order to provide a safety parameter and to predict effectiveness of the treatment. Various thermometry methods are available and have provided a large body of data, however the methods are expensive and demanding for the user. The power output [35] and temperatures reached during mEHT are lower than those achieved during conventional hyperthermia [33] and the toxicity associated with mEHT is not significant. The application of thermometry during mEHT is therefore not necessary as a safety parameter when treating cervical tumors.

As the treatment is effective, even under low temperatures and low power, the use of thermometry to predict effectiveness is not considered relevant during mEHT. The authors therefore suggest that the applied cumulative energy (power-on-time) might be more suitable as a dosing parameter during mEHT, as any non-thermal effects should be dependent on the exposure time of the amplitude-modulated RF.

## **Quality of life**

These results show an improved functioning and symptom experience associated with the addition of mEHT and an improved QoL associated with local control. A complete response increases participant's ability to return to normal functioning status sooner, ultimately reducing the social burden of the disease.

## Conclusion

The addition of mEHT applied at a low power of 130 W to CRT did not result in any unacceptable treatment-related toxicity in our high-risk (HIV-positive and partly obese) patient sample. The toxicities directly related to mEHT were mild and did not compromise the dose or timing of the cisplatin or RT. mEHT is therefore a safe adjunct to CRT protocols in HIV-positive participants and in a resource-constrained setting. This report is an important contribution to the field of knowledge in mEHT and provides important safety data for the use of mEHT in high risk populations, in the absence of sophisticated thermometry and planning technologies, providing evidence of the safety and efficacy of a technology that can easily be incorporated into general practices.

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