Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia

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ABSTRACT

Adding hyperthermia to standard radiotherapy (RT + HT) improves treatment outcome for patients with locally advanced cervical cancer (LACC). We investigated the effect of hyperthermia dose on treatment outcome for patients with LACC treated with RT + HT.

We collected treatment and outcome data of 420 patients with LACC treated with hyperthermia at our institute from 1990 to 2005. Univariate and multivariate analyses were performed on response rate, local control, disease-specific survival and toxicity for these patients to search for a thermal dose response relationship.

Besides commonly identified prognostic factors in LACC like tumour stage, performance status, radiotherapy dose and tumour size, thermal parameters involving both temperature and duration of heating emerged as significant predictors of the various end-points. The more commonly used CEM43T90 (cumulative equivalent minutes of T90 above 43 °C) was less influential than TRISE (based on the average T50 increase and the duration of heating, normalised to the scheduled duration of treatment).

CEM43T90 and TRISE measured intraluminally correlate significantly and independently with tumour control and survival. These findings stimulate further technological development and improvement of deep hyperthermia, as they strongly suggest that it might be worthwhile to increase the thermal dose for LACC, either by treatment optimisation or by prolonging the treatment time. These results also confirm the beneficial effects from hyperthermia as demonstrated in our earlier randomised trial, and justify applying radiotherapy and hyperthermia as treatment of choice for patients with advanced cervical cancer.

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1. Introduction

At our department patients with locally advanced cervical cancer (LACC) have been treated with combined radiotherapy and hyperthermia (RT + HT) since 1990. From 1990 to 1996 a randomised trial was conducted, in which radiotherapy alone was compared to RT + HT for the treatment of locally advanced pelvic tumours.[1] It showed a significant improvement in local control and overall survival with the addition of hyperthermia. The improvement was most apparent for

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patients with LACC[2], and a recent update showed that the improvement is persistent after 12 years follow-up.[3] After the randomised trial was completed, RT + HT became a standard treatment approach for patients with LACC in the Netherlands.[4]

From the clinical studies thus far performed, it is clear that RT + HT improves treatment outcome compared to radiotherapy alone. However, as the pelvic tumour control rate is still only 53% at five years[4], there is still a strong need to search for ways to improve our treatment strategy. As has previously been shown for radiotherapy dose escalation and the addition of chemotherapy to RT + HT, we anticipate that optimising the thermal dose delivered may further improve treatment results in this patient group.[5–8]

For a variety of other tumour types that are treated with radiotherapy and superficial hyperthermia, various thermal dose parameters have been shown to relate to treatment outcome significantly.[9–17] For deep hyperthermia, much less is known about the relationship between temperatures measured during treatment and treatment outcome.[18–21]

In this report we present the results of the retrospective evaluation on which thermal dose parameters are of prognostic value for treatment outcome when patients with LACC are treated with RT + HT. We investigated the relation between various thermal dose parameters and complete response rate, pelvic tumour control, disease-specific survival and acute and late toxicities.

2. Patients and methods

From May 1990 to July 2005 458 patients with LACC were treated with RT + HT at the Erasmus Medical Center Rotterdam. For 420 patients, temperature and power data are available. For 38 patients, temperature and power data were inaccessible.[22]

2.1. Patients

Patients were eligible for RT + HT if they required primary standard radiotherapy for cervix cancer FIGO (International Federation of Gynaecology and Obstetrics) stage IB2–IV. For staging, we used the 4th edition of the UICC TNM Classification of malignant tumours. In all patients, diagnosis was confirmed by histopathological examination. All patients received a standard diagnostic work-up including a gynaecologic examination under anaesthesia with a cystoscopy, a CT-scan of the abdomen and a chest X-ray. An acceptable cardiac condition defined as ASA (American Society of Anesthesiologists) classification of 2 or less was required and patients' expected survival had to exceed 6 months. Patients with a pacemaker or a metal implant in the pelvic region larger than 10 cm were excluded, since these are absolute contraindications for hyperthermia.

2.2. Radiotherapy

Radiotherapy was prescribed in accordance with the Dutch Society for Radiotherapy and Oncology guidelines. External beam radiotherapy was given in 23–28 daily fractions of 2.0–1.8 Gy, five times a week, to a total dose of 46.0–50.4 Gy using a four-field box technique with 6–23 MV photons. The para-aortic region was included in case of positive lymph nodes along the common iliac artery or aorta. An additional pelvic sidewall boost was given to patients with residual tumour in the parametrium at the time of first brachytherapy. Twenty-two patients received chemotherapy prior to radiotherapy because of positive lymph nodes or bulky tumour load.

Brachytherapy was scheduled for all patients and was delivered using Iridium-192 (HDR) to a total dose of 17 Gy, applied in two fractions, or 18–21 Gy in three fractions or 30 Gy in 60 h (LDR). Dose specifications and target volume definition were according to the International Commission on Radiation Units and Measurements (ICRU) report 50. Further details have previously been published.[4]

2.3. Hyperthermia

Deep hyperthermia was prescribed once weekly to a total of five times during the 5 weeks of external beam radiotherapy. For all hyperthermia treatments the BSD-2000 system was used (BSD Medical Corporation, Salt Lake City, Utah, USA), with the Sigma-60 or Sigma-Eye applicator depending on the patients' size.[23]

For thermometry Bowman probes were placed in bladder, rectum and vagina. Thermal mapping was performed every 5 min with a step size of 1 cm and a maximum map length of 14 cm. The standard prescribed duration of a treatment was 90 min, during which time temperatures were increased to as high and homogeneous as patient tolerance and normal tissue temperatures permitted: normal tissue temperatures should not exceed 43 °C during the first 60 min of a treatment, and not exceed 44 °C during the last 30 min. Besides the measured temperatures, information on too high temperatures (hotspots) came from the patient. Patients were carefully instructed to mention any uncomfortable feelings that could be suggestive of hotspots during treatment. If such complaints occurred, treatment settings such as phase, amplitude, frequency and power were adjusted to alleviate the complaints.

2.4. Temperature and power measures

Based on the temperatures measured intraluminally, several treatment parameters were calculated using RHyThM (Rotterdam Hyperthermia Thermal Modulator), which has been described elsewhere in detail.[24] The hyperthermia-related parameters are described in Table 1. Cumulative Equivalent Minutes of T90 at 43 °C (CEM43T90) is a mathematical description of the exponential relationship found *in vivo* and *in vitro*, between temperature and exposure time; it is calculated as follows:[22]

$$CEM43T90 = \sum_{n=1}^{n=5} \int_0^{90} \Delta t R^{(43-T90)}$$

n is the number of treatments; Δt is the time interval of treatment (min); T90 is the average all lumen T90 during Δt; R is a constant; when $T > 43$ °C $R = 0.5$, when $T > 43$ °C $R = 0.25$.

Table 1 – Description of thermal parameters.	
Abbreviation	Parameter description
ALT20	Temperature exceeded by 20% of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient (All Lumen **T20**)
ALT50	Temperature exceeded by 50% of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per (All Lumen **T50**)
ALT90	Temperature exceeded by 90% of monitored sites in bladder, vaginal and rectal lumen together and averaged over all treatments per patient (All Lumen **T90**)
VT50	Temperature exceeded by 50% of monitored sites in the whole vaginal lumen and averaged over all treatments per patient (Vagina **T50**)
BT50	Temperature exceeded by 50% of monitored sites in the whole bladder lumen and averaged over all treatments per patient (Bladder **T50**)
RT50	Temperature exceeded by 50% of monitored sites in the whole rectal lumen and averaged over all treatments per patient (Rectum **T50**)
NIP	Mean Net Integrated Power, averaged over all treatments[*]
CEM43T90	Cumulative equivalent minutes at a T90 of 43 °C as described by Rau et al.[21]
TRISE	Custom made thermal dose parameter based on ALT50 and duration of heating

NIP(mean Net Integrated Power) : $\sum_{t=0}^{t=\max} \int (P_{forward} - P_{reflected}) \times \Delta t$

$t = 0$ is start of treatment, $t = \max$ is end of treatment, $P_{forward}$ is the power forwarded during Δt, $P_{reflected}$ is the power reflected during Δt and Δt is the time period of measurement.

In our treatment schedule only T90 is a real independent variable for each patient. The overall heating time cannot be considered as such because the number of treatments and the duration of a treatment are prescribed a priori, i.e. five times and 90 min. Hence, we anticipated that a thermal dose parameter expressing the temperature as dose but with the actual treatment time normalised to the overall treatment time of 450 min may be a worthwhile parameter to investigate.

TRISE incorporates temperature and duration of heating, but instead of transposing the measured temperatures to equivalent minutes at a reference temperature, we simply multiplied the T50 increase above 37 °C during treatment with the duration of treatment for all treatments, and normalised it to 450 min; the scheduled total treatment time for all patients.

$$\text{TRISE} = \frac{\sum_{n=1}^{n=\max} (\text{ALT50} - 37°C) \times dt}{450}$$

n is the number of treatments; dt is the duration of treatment; ALT50 is the lumen T50, Table 1.

2.5. Treatment outcome

Follow-up visits were planned in accordance with the Dutch Association of Cancer Centers Guidelines. Information on complete response, local control, survival and late toxicities were gathered retrospectively.

Complete response rate was defined as the complete disappearance of tumour within the irradiated volume and was assessed by anamnestic information, gynaecological examination and supplemental investigations if indicated. Patients who did not achieve a complete response were considered pelvic failures at day 0.

Duration of pelvic tumour control was defined either as the time elapsed since the date of the last radiotherapy fraction and the date of local recurrence within the irradiated volume, or death of any cause.

Disease-specific survival was defined as the time between date of the last fraction of radiotherapy and death due to cancer-related cause, treatment-induced toxicity or last follow-up.

For acute hyperthermia-related toxicity analysis, the worst grade toxicity a patient developed was included in this analysis. The grading system used for acute hyperthermia-related toxicity is described in Table 2. Acute hyperthermia-related toxicity was defined as symptoms developing within 24 h after a hyperthermia treatment.

Late radiation-induced toxicity was defined as toxicity due to treatment that occurred at least 3 months after the last fraction of radiotherapy and was classified according to the CTC (Common Toxicity Criteria) scale, version 3. Patients who developed a local recurrence were censored at the time of recurrence.

2.6. Statistical analysis

The primary end-points were complete response rate, pelvic tumour control and disease-specific survival.

Secondary end-points were acute hyperthermia-related and late radiation-induced toxicities.

For the thermal dose analyses, only patients were included for whom temperature measurements were available for at least 50% of the treatments they received, to ensure the temperature measures depict a patients' treatment accurately. For patients with treatments without thermometry, the total thermal dose was obtained through adding the average temperature dose of all treatments with thermometry. This concerned 221 treatments in 128 patients.

In the temperature analyses, all patients were included, because variation between treatments is relatively small. In contrast to TRISE, CEM43T90 was not normally distributed, so its natural logarithm (lnCEM43T90) was entered in the analyses.

The following baseline characteristics were entered in univariate analysis (Table 3): FIGO stage of the tumour, World Health Organisation performance status (WHO-PS), lymph node status (N-status), histology, patient age, having received

Table 2 – Grading system used for classification of acute hyperthermia-related toxicity.	
Grade	Definition
1	Symptoms caused by hyperthermia treatment that lasted less than 3 days
2	Symptoms caused by hyperthermia treatment that lasted 3–14 days
3	Symptoms caused by hyperthermia treatment lasting 14 days or longer, or causing a delay or interruption of treatment
4	Symptoms caused by hyperthermia treatment that required surgery

induction chemotherapy and tumour size. For radiotherapy dose, we entered a bivariate parameter indicating whether radiotherapy was given and completed as prescribed, i.e. 23–28 daily fractions of 2.0–1.8 Gy external beam radiotherapy combined with LDR, PDR or HDR brachytherapy at their appropriate schedules, or not (RTc).

To ensure fair-sized subgroups, FIGO stage and WHO-PS were regrouped for the multivariate analyses; FIGO stages IIA and B were taken together (equivalent to T2 of the TNM classification) as were FIGO stages IIIA and IIIB (T3 of the TNM classification). WHO-PS was regrouped as WHO 0 or larger than 0.

For the toxicity analyses, the subcutaneous fat thickness, patients' anterior-posterior and lateral diameter were also entered. These measures were determined on the CT-scan made

Table 3 – Patient, tumour and treatment characteristics.			
FIGO stage	IB2	14	(3%)
	IIA	27	(6%)
	IIB	146	(35%)
	IIIA	21	(5%)
	IIIB	158	(38%)
	IVA	54	(13%)
N-status	Nx	47	(11%)
	N0	239	(57%)
	N1	134	(32%)
Histology	SCC	358	(85%)
	AC	38	(9%)
	Other	20	(5%)
	Unknown	4	(1%)
WHO-PS	0	262	(62%)
	1	123	(29%)
	2	33	(8%)
	3	2	(1%)
Chemotherapy	Yes	22	(5%)
	No	398	(95%)
RTc	Yes	360	(86%)
	No	60	(14%)
Number of HT	1	15	(3%)
	2	16	(4%)
	3	17	(4%)
	4	73	(16%)
	5	299	(73%)
Age	Mean	57 years	(22–89)
Overall treatment time	Mean	40.5 days	(7–115)
Tumour size	Mean	8.9 cm	(3.9–16.5 cm)

FIGO, International Federation of Gynaecology and Obstetrics; N-status, lymph node status; SCC, squamous cell carcinoma; AC, adenocarcinoma; WHO-PS, World Health Organisation Performance Status; RTc, radiotherapy completed as planned (yes) or not (no); HT, hyperthermia treatments.

for treatment planning. For each significant thermal parameter, multivariate models were constructed incorporating all significant baseline characteristics on any end-point.

For analyses on response rate and acute hyperthermia-related toxicity, logistic regression was used. Cox regression was used for analyses on pelvic tumour control, disease-specific survival and late toxicity. P-values below 0.05 were considered significant.

For depicting the relationship between thermal dose and treatment outcome (Fig. 1), we grouped the thermal dose parameters at their 20th percentiles.

3. Results

Baseline characteristics of the 420 patients with LACC are summarised in Table 3.

3.1. Thermal parameters

Hyperthermia treatment parameters are summarised in Table 4. Overall, the temperatures measured are comparable to what we and others found previously with an ALT50 of 40.6 °C.[19,22] The CEM43T90 was relatively low and showed wide variation, with a mean of 5.05. Our new parameter TRISE was 2.96 on average. Correlation between various thermal parameters is shown in Table 5.

Complete response rate (CR-rate): Three hundred and twenty-nine patients (78%) achieved a complete response following RT + HT, 65 (16%) patients had a partial response, 13 (3%) stable disease and 5 (1%) patients had progressive disease during treatment. For 8 patients, no information on tumour response could be gathered (2%). FIGO stage, tumour size, N-status, WHO-PS and RTc emerged as significant baseline characteristics from the univariate analysis (Table 6a). The mean intraluminal temperature measured (ALT50) for complete responders (CRs) was similar to that of the non-complete responders (NCRs) (40.5 °C and 40.6 °C, respectively). There was a slight difference in CEM43T90 between the CRs and the NCRs; 5.23 versus 4.35. Of the thermal parameters, TRISE and lnCEM43T90 were significant. In multivariate analysis, the influence of lnCEM43T90 lost its significance ($p = 0.195$), but TRISE remained significant ($p = 0.013$). The CR-rate per thermal parameter group is depicted in Fig. 1a.

3.2. Pelvic tumour control (PTC)

PTC was 65% (95% confidence interval (CI) 60–70%) one year after treatment, and 53% (95% CI 47–58%) at five years. From univariate analysis, FIGO stage, tumour size, N-status, age, WHO-PS and RTc emerged as significant baseline characteristics (Table 6a).

Table 4 – Hyperthermia treatment parameters.

Parameter	Average	Standard deviation
ALT20	41.1 °C	0.31
ALT50	40.6 °C	0.55
ALT90	39.8 °C	0.55
VT50	40.3 °C	0.74
BT50	40.8 °C	0.61
RT50	40.6 °C	0.51
NIP	630 kJ	126
CEM43T90	5.05 min	4.18
TRISE	2.96 °C	2.96

Table 5 – Pearson's correlation coefficients of thermal parameters.

	CEM43T90	TRISE	NIP
ALT20	0.36	0.31	0.07
ALT50	0.76	0.54	−0.04
ALT90	0.77	0.53	−0.02
VT50	0.72	0.43	−0.09
RT50	0.65	0.43	0.11
BT50	0.65	0.54	0.04
NIP	−0.05	0.19	xx
TRISE	0.65	xx	0.19

The mean intraluminal temperature measured (ALT50) for patients who developed a pelvic failure was similar to that of patients who did not (40.5 °C and 40.6 °C, respectively). There was a slight difference in CEM43T90 between the two groups; 4.40 versus 5.50. After adjustment for other significant factors, lnCEM43T90 and TRISE remained of significant influence ($p = 0.019$ and 0.021, Table 6b). The 3-year PTC rate per thermal parameter group is depicted in Fig. 1b.

Table 6a – Univariate analysis for patient and tumour characteristics and thermal parameters on complete response rate (CR-rate), pelvic tumour control (PTC) and disease-specific survival (DSS) (p-values).

	CR-rate	PTC	DSS
FIGO stage	**0.000**	**0.000**	**0.000**
N-status	**0.027**	**0.034**	**0.047**
Tumour size	**0.000**	**0.022**	**0.002**
Histology	0.050	0.374	0.209
WHO-PS	**0.000**	**0.000**	**0.001**
Age	0.319	**0.037**	0.166
Chemotherapy (yes or no)	0.092	0.103	0.240
RTc	**0.000**	**0.000**	**0.000**
OTT (days)	0.246	0.185	0.671
ln CEM43T90	**0.025**	**0.002**	**0.002**
TRISE	**0.000**	**0.000**	**0.000**
NIP	0.070	**0.015**	**0.007**
ALT20	0.683	0.051	**0.036**
ALT50	0.878	0.108	**0.038**
ALT90	0.990	0.091	**0.048**
VT50	0.259	0.424	0.125
BT50	0.795	**0.043**	0.062
RT50	0.479	0.098	**0.027**

3.3. Disease-specific survival (DSS)

DSS was 75% one year after treatment (95% CI: 71–79%) and 47% at 5 years (95% CI: 41–53%). Significant baseline characteristics in univariate analysis were again FIGO stage, tumour size, N-status, WHO-PS and RTc (Table 6a). CEM43T90 for patients who ultimately died of cervical cancer was 4.45 on average and 5.47 for patients who did not die of cervical cancer. The ALT50 was again comparable in both groups, 40.5 °C versus 40.6 °C. After adjustment for significant baseline characteristics in multivariate analysis, lnCEM43T90 and TRISE remained of significant influence on DSS ($p = 0.001$ and 0.002, Table 6b). The 3-year DSS rate per thermal parameter group is depicted in Fig. 1c.

3.4. Acute hyperthermia-related toxicity

One hundred and fifty-three patients developed acute hyperthermia-related toxicity to the subcutaneous tissues. Fifty-one percent of patients (80/153) were grade 1, 39% grade 2 (60/153), 9% were grade 3 (16/153) and only one patient required a surgical intervention due to her subcutaneous burn (0.6% grade 4). In univariate analysis, the mean power applied (NIP) was significant as well as TRISE (Table 7). Patients who developed acute hyperthermia-related toxicity received 46 kJ more than those who did not and their TRISE was 1.7 °C higher. Because of the expected mechanism behind the development of subcutaneous burns, extra anatomy-related factors were entered in univariate analysis, such as the thickness of the subcutaneous fat and the patients' size. In patients who developed toxicity the dorsal subcutaneous fat was thicker (0.7 cm) and they were larger in anterior-posterior (0.9 cm) and lateral (1.5 cm) directions. After adjustment for these factors, NIP lost its significant influence, but TRISE did not ($p = 0.010$).

Fourteen patients developed complaints related to the peripheral nervous system during and/or after a hyperthermia treatment. For 12 patients, complaints were restricted to CTC grade 2, and five developed grade 3 neurotoxicity. A detailed description and evaluation of significant factors influencing neurotoxicity after deep hyperthermia was previously published.[25]

3.5. Late radiation-related toxicity

CTC grade 3 or higher was diagnosed in 6% of patients in the first year after treatment, and in 12% of patients at 5 years after treatment (95% CI: 7–17%). Of all factors studied, only patient size was of significant influence on long-term radiotherapy-induced toxicity, both in the AP direction and in the lateral direction ($p = 0.01$ and $p = 0.02$).

4. Discussion

To our knowledge, this study is the largest study investigating the relation between various simple and complex thermal dose parameters and complete response rate, pelvic tumour control, disease-specific survival and acute and late toxicities in patients with LACC treated with RT + HT.
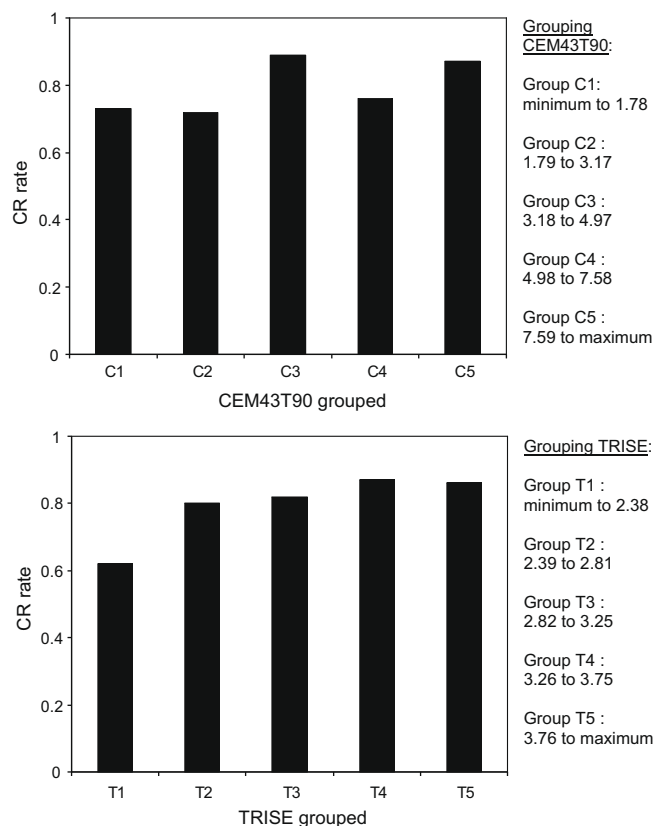
Fig. 1a – Complete response rate (CR-rate) per thermal dose parameter group.

Table 6b – Multivariate analysis after adjustment for other significant factors (p-values).			
	CR-rate	PTC	DSS
ln CEM43T90	0.195	**0.019**	**0.001**
TRISE	**0.027**	**0.021**	**0.002**
NIP	0.757	0.129	0.060
ALT20	0.891	0.320	0.212
ALT50	0.331	0.702	0.318
ALT90	0.323	0.685	0.370
VT50	0.194	0.942	0.354
RT50	0.810	0.510	0.166
BT50	0.347	0.565	0.645

FIGO, International Federation of Gynaecology and Obstetrics; N-status, lymph node status; WHO-PS, World Health Organisation Performance Status; RTc, radiotherapy completed as planned or not; ln CEM43T90, natural logarithm of CEM43T90.

We found a significant relationship between those thermal parameters that include both height of temperature and duration of heating (CEM43T90 and TRISE) and all disease control end-points. After adjustment for other correlating factors in multivariate analysis, TRISE remains significantly correlated with response and survival and CEM43T90 with survival.

Overall, treatment outcome is relatively meager than other published series, both since and before 1996. It was a major point of criticism of the Dutch Deep Hyperthermia Trial (DDHT) and can be explained by the bad prognostic characteristics of the patients that were included in the trial.[2] The
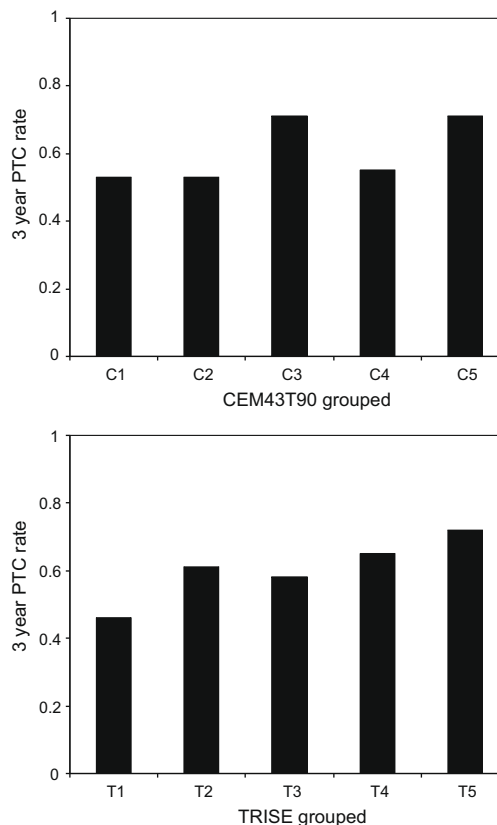

Fig. 1b – 3-Year pelvic tumour control (PTC) rate per thermal dose parameter group.
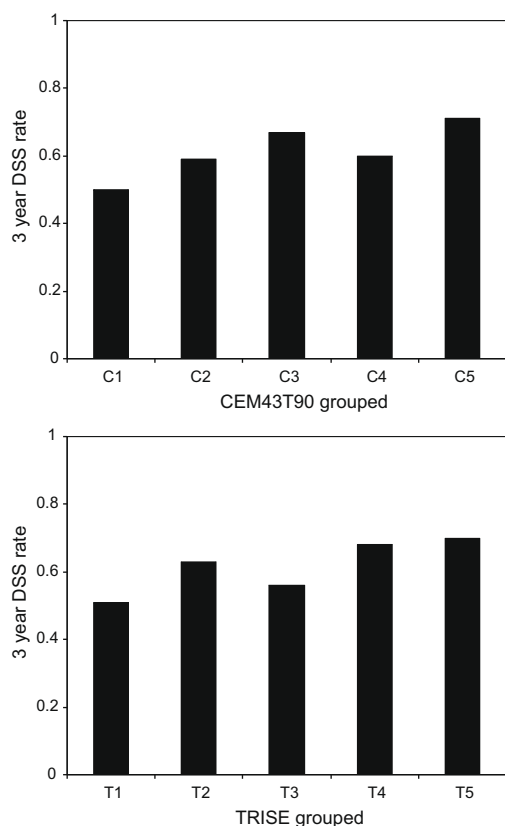
Fig. 1c – 3-Year disease-specific survival (DSS) rate per thermal dose parameter group.

Table 7 – Univariate analysis for acute hyperthermia-related skin/subcutaneous toxicity.

	p-Value
FIGO stage	0.362
N-status	0.118
Tumour size	0.942
Histology	0.484
WHO-PS	**0.046**
Age	0.953
Chemotherapy (yes or no)	0.363
OTT (days)	0.219
RTc (yes or no)	**0.025**
Thickness subcutaneous fat dorsal	**0.004**
Ventral	0.072
Lateral	0.360
Patient size anterior to posterior	**0.008**
Patient size lateral to lateral	**0.001**
ln CEM43T90	0.234
TRISE	**0.002**
NIP	**0.000**
ALT20	0.911
ALT50	0.377
ALT90	0.728
VT50	0.061
RT50	
BT50	0.061

FIGO, International Federation of Gynaecology and Obstetrics; N-status, lymph node status; WHO-PS, World Health Organisation Performance Status; OTT, overall treatment time; RTc, radiotherapy completed as planned or not.

same applies to the patient population presented here. Even more: since we have shown the large benefit of the addition of hyperthermia to radiotherapy, we tend to accept patients who are older, have larger tumours and are in worse general condition compared to the period of the DDHT.[4] Large tumour, older age and worse general condition have a negative influence on treatment outcome for patients with cervical carcinoma, as was previously shown by others.[7,26–30]

For the patient group presented here, there is no real control group to which we can compare the results. What we have done is an evaluation of the results compared to those in the RT + HT arm in the DDHT. We found that, after adjust-

ment for differences in prognostic factors, the results are similar and indirectly confirm the beneficial effects from hyperthermia that we have shown in our earlier randomised trial.[4]

Other researchers have previously shown a similar beneficial effect of adding hyperthermia to standard radiotherapy for LACC (Table 8). Only one[35] of six randomised trials showed no beneficial effect of adding hyperthermia and this trial was heavily criticised because of flaws in its design and inadequate heating techniques.[35–37]

The combination of chemotherapy and radiation is currently the standard of treatment in most countries, but recently a meta-analysis based on individual patient data

Table 8 – Randomised studies comparing RT to RT + HT for locally advanced cervical cancer.

	FIGO	*n*	CR-rate		Pelvic control		Overall survival	
			RT	RT + HT	RT	RT + HT	RT	RT + HT
Datta[31]	IIIB	64	58	74	46	67[a]	73	81[a]
Sharma[32]	II, III	50			50	70[b]		
Hong Wei[33]	IIB, IIIB	120	48	72*				
Harima[34]	IIIB	40	50	80*	49	80[c,]*	48	58[c]
Vasanthan[35]	IIB–IV	110			∼80	∼70[c]	73	73[c]
DDHT[2,3]	IIB–IV	114	57	83*	37	56[d,]*	20	37[d,]*

* Significant difference.
a At 2 years.
b At 1.5 years.
c At 3 years.
d At 12 years.

further strengthens earlier suggestions that the addition of chemotherapy to radiotherapy is less beneficial in the higher stages, while hyperthermia has shown its additional value especially in the higher stages.[38,39]

Many of the parameters that we found to be of prognostic importance in our patient group are known prognostic factors for patients with cervical carcinoma. FIGO stage, tumour size measured on CT-scan, lymph node status, general condition, patient age and radiation dose are known prognostic factors for patients with cervical carcinoma. The prognostic importance of hyperthermia dose, even after adjustment for all other prognostic factors, is a new finding in this study. Previous research in this area was limited to populations too small to allow for a multivariate analysis.[18–21]

The finding of a thermal dose effect relationship for dose parameters derived from intraluminal measurements is further important for deep hyperthermia treatment guidelines. Apparently, interstitial measurements are not required to monitor the quality of treatment for cervical cancer.

Our finding of a thermal dose effect relationship suggests that the clinical outcome of RT + HT for LACC can be improved by an increase in thermal dose (Fig. 2). The dose-effect curve in Fig. 2 was constructed using the coefficients, $\beta0$ and $\beta1$, found in univariate analysis. From this figure, we can hypothesise that adding one treatment to the current schedule, results in a 4% increase in the probability of a complete response for patients who receive the average TRISE dose or less.

Naturally, a higher dose can be achieved in two ways; higher temperatures, or longer duration of heating. We do not expect to achieve higher temperatures with our currently used strategy as it already aims at heating to maximum patient tolerance. To further increase temperature, hyperthermia treatment planning may be a useful tool.[40] Wust et al. conducted a simulation study and concluded that an increase in T90 of 1.9 °C can be achieved with temperature optimisation using hyperthermia treatment planning. However, data on the clinical effectiveness of hyperthermia treatment planning are limited to date. In view of our current and previous results, longer duration of heating seems a worthwhile option to explore, especially for patients in the lower thermal dose groups.

In conclusion, the results of this large group of patients treated with RT + HT, confirm the results of RT + HT that we have seen in the DDHT and form an external validation of that trial. Currently, combined radiotherapy and cisplatin is considered a standard treatment for patients with cervical carcinoma worldwide. However, we also find it justified to combine radiotherapy with hyperthermia instead of cisplatin, since the beneficial effects of both modalities are of the same magnitude.[41] In any case, we strongly recommend RT + HT for patients with a contraindication for cisplatin, due to e.g. poor general condition, insufficient renal function or extended field radiotherapy and many Dutch radiotherapy institutes have adopted this view since 1996.

The situation in the Netherlands, where in fact two standard treatment approaches coexist for locally advanced cervical cancer, gives us the unique opportunity to compare the two approaches. In an ongoing Dutch multicenter phase III trial, the two combined treatments are compared questioning which patients benefit most from which additional treatment. Another interesting question is of course whether the effect of radiotherapy plus cisplatin can be further improved by the addition of hyperthermia to the treatment schedule. This question is addressed in an international multicenter phase III trial.

Conflict of interest statement

None declared.

Acknowledgements

$$p(CR) = 1 / (1 + EXP(- \beta_1 * X1 + \beta_0)) = 1 / (1 + EXP (-0.607 * TRISE - 0.369)$$
β_0 and β_1 are the coefficient and constant derived from univariate analysis

Legend:
- ✳ Real data points collected from this series
- ○ p(CR) for TRISE = 0 derived from Dutch Deep Hyperthermia Trial (0.57)
- ⋯ p(CR) for mean TRISE + estimated improvement upon adding 1 extra HT = 0.87
- —·— p(CR) for mean TRISE = 0.83

Fig. 2 – Complete response probability or p(CR) as a function of TRISE.

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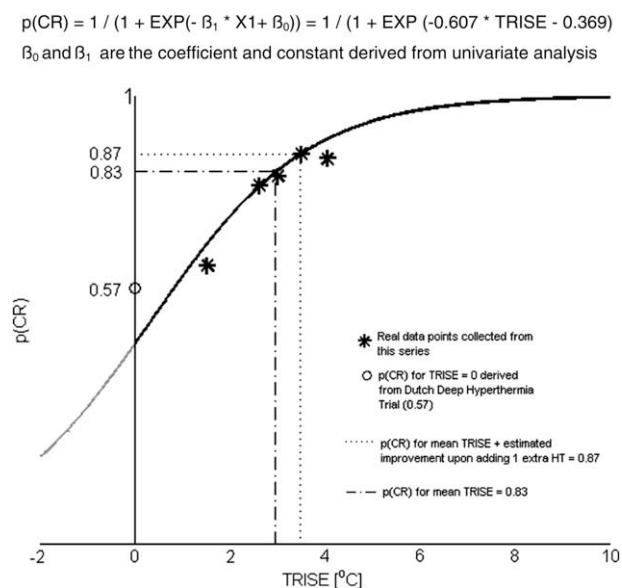
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