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Original Article

Confirmation of thermal dose as a predictor of local control in cervical carcinoma patients treated with state-of-the-art radiation therapy and hyperthermia

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ABSTRACT

Background: Addition of deep hyperthermia results in improved local control (LC) and overall survival (OS) compared to radiotherapy alone in patients with cervical carcinoma. Previously, we showed that the thermal dose of hyperthermia significantly correlates with LC and disease specific survival (DSS). Over the last decade, new radiation techniques were introduced resulting in improved LC.
Aim: To validate the effect of thermal dose in a more recent cohort of patients treated with modern radiotherapy techniques, including image guided brachytherapy (IGBT).
Methods: We analyzed primary cervical carcinoma patients treated with a combination of radiotherapy and deep hyperthermia between 2005 and 2016 at our institute. Data on patient, tumor and treatment were collected including the thermal dose parameters TRISE and CEM43T90. Follow-up data on LC, disease free survival, DSS, OS as well as late toxicity data were collected. Data were analyzed using the Cox proportional hazard and Kaplan–Meier analyses.
Results: 227 patients were included. In multivariate analysis, histology, FIGO stage, lymphadenopathy, TRISE, CEM43T90 and IGBT had a significant effect on LC. In the patients treated with IGBT, the thermal dose parameter TRISE remained to have a significant effect on LC in univariate analysis.
Conclusions: The positive association between thermal dose and clinical outcome is replicated in an independent, recent cohort of cervical carcinoma patients. Importantly, in patients receiving IGBT, the effect of thermal dose on clinical outcome is still observed.

Cervical carcinoma is the sixth most common cancer in woman in The Netherlands and the fourth most common cancer in woman worldwide [1]. Radiotherapy remains the cornerstone of treatment for women with a locally advanced cervical carcinoma [2]. Chemotherapy and hyperthermia are effective sensitizers of radiotherapy in these patients, resulting in improved overall survival (OS). Addition of hyperthermia to radiotherapy results in local control (LC) and OS rates comparable to chemoradiotherapy in patients with large FIGO IIB or higher FIGO stage tumors [2–8].

Hyperthermia, defined as an elevation of tumor temperature in the range of 40–44 °C, is a potent sensitizer of radiation therapy [9,10]. The thermal enhancement of hyperthermia depends on the thermal dose, which is the net result of the temperature rise in the tumor and the duration of the heating [11]. The achieved thermal dose in a particular patient is influenced by several factors including patient condition, patient comfort and technical possibilities to steer the energy deposition. Thermal dose parameters considered to be related with treatment outcome are: CEM43T90 (cumulative equivalent minutes of T90 above 43 °C) and our linearized version TRISE [11,12]. We have previously shown a dose dependent effect of CEM43T90 and TRISE on LC and OS in 420 patients treated with thermoradiotherapy between May 1990 and July 2005 [11].

In the last decade several improvements in the treatment of cervical carcinoma patients have taken place, both globally as well as in our institute. At our institute, the more conformal radiotherapy techniques intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) were introduced, along with a plan-of the-day protocol [13]. These techniques allow adequate target

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coverage, while reducing dose to the adjacent organs [13,14]. Second, introduction of image—MRI—guided brachytherapy (IGBT) results in more conformal and higher dose to the tumor, leading to improved LC, disease specific survival (DSS) and OS with acceptable toxicity [15–20]. IGBT was introduced at our institute in 2012.

Besides improvements in radiotherapy techniques, technological developments in hyperthermia delivery techniques have been implemented. In 2011 SAR-based hyperthermia treatment planning (HTP) guided steering was introduced for all deep hyperthermia patients at our institute [21]. In a cross over study we showed that with HTP guided steering, the thermal dose achieved was comparable to our empirical steering protocol. Further, HTP guided steering holds the promise to predict treatment quality and of patient-specific optimization and real-time complaint alleviation [22].

We are not aware of any studies confirming our previously found association between thermal dose and clinical outcome in cervical carcinoma patients. In addition, the effect of thermal dose in patients treated with IGBT, leading to improved LC, is unknown. The aim of this study was to determine the effect of thermal dose on clinical outcome in an independent, more recent cohort. In addition, we specifically analyzed the effect of thermal dose in the patients treated with state-of-the-art IGBT.

Methods

Patient population

The research protocol for this investigation was approved by the medical ethics committee of Erasmus MC, University Medical Center Rotterdam (MEC-2018-1081). Patients included were diagnosed with primary cervical cancer and treated with curative intent using thermoradiotherapy at our institute between July 2005 and December 2016. Excluded were patients receiving concurrent chemotherapy, fewer than four of the five intended hyperthermia sessions and patients receiving radiotherapy at other institutes because of a lack of data on follow-up. All patients had a histologically confirmed cervical carcinoma and were staged by the International Federation of Gynaecology and Obstetrics (FIGO) clinical staging system, including investigation under general anesthesia with cystoscopy and lymph node staging using CT and/or MRI and/or PET-CT.

Indications for primary thermoradiotherapy at the Erasmus MC Cancer Institute are locally advanced tumors: 'lateral' FIGO IIB (>50% parametrial invasion), IIIA, IIIB and IVA. In addition, patients with inoperable tumors and a contra-indication for, or refusing cisplatin-based chemotherapy are also treated with thermoradiotherapy. Patients with a local tumor equal to or larger than 6 cm and/or large para-aortic (>1 cm) or iliac (>2 cm) lymphadenopathy were treated upfront with induction chemotherapy, followed by standard thermoradiotherapy [23]. Induction chemotherapy consists of 6-weekly cycles of cisplatin/taxol chemotherapy, with clinical assessment after 3 and 6 cycles.

Radiotherapy treatment

Radiotherapy consisted of daily external beam radiotherapy (EBRT) 23×2 Gy for pelvic fields or 28×1.8 Gy if the para-aortal region was included. EBRT was delivered using 3D conformal techniques until 2011, after which intensity modulated radiotherapy (IMRT) was introduced. From 2014 onwards volumetric arc therapy (VMAT) was the preferred technique, because of even better conformity and faster treatment times. From 2011 onwards a plan-of-the day protocol was introduced to adapt the plan to the position of the uterus, thereby decreasing dose to bowel and bladder [13]. A brachytherapy boost was delivered using a high-dose rate iridium source using 2D planning to point A, with a dose of $2 \times 8{,}5$ Gy. From the end of 2012 onwards, image (MRI) guided brachytherapy (IGBT) was applied with a combined interstitial and intracavitary approach, delivering 3 or 4 fractions of 7 Gy or more to the high-risk CTV [20].

Hyperthermia treatment

Hyperthermia (HT) was delivered after radiotherapy, a total of five times during the 5–6 weeks of EBRT. The BSD-2000 system (Pyrexar Medical Corporation, Salt Lake City, Utah, USA) was used for all HT treatments, with the Sigma-60 or Sigma-Eye applicator selection depending on the patients' size. Intraluminal thermometry was performed by placing thermometers in rectum, bladder and vagina for all patients. Until July 2012 thermometry was performed by using Bowman probes (Pyrexar Medical Corporation, Salt Lake City, Utah, USA) combined with thermal mapping every 5 min during treatment with a step size of 1 cm and a maximum length of 14 cm. Hereafter temperature measurement was continuous using multi-sensor fiber optic temperature probes (FISO Technologies Inc., Québec, QC, Canada, 4–8 sensors with a distance between sensors of 2 cm). Both systems fulfill the quality assurance guidelines of European Society for Hyperthermic Oncology, accuracy ±0.2 °C [24,25]. The 90 minutes scheduled treatment time consists of a 30 min warm up period to intraluminal temperatures of $\geq$40 °C. Then treatment was continued for 60 min aiming for maximum intraluminal temperatures depending on patient tolerance.

Collection patient and follow-up data

The following patient characteristics were extracted from the patients' files: age at diagnosis, histology, FIGO stage and lymph node status. Local FIGO stage was noted except for 6 patients presenting with limited distant metastases—but treated with curative intent—which were recorded as FIGO IVB. Radiotherapy and HT treatment characteristics were extracted from treatment planning and other recording systems.

Pelvic recurrence, distant recurrence, survival status, date and cause of death, as well as late toxicity data were extracted and/or retrieved from patient records, referring hospitals, general physicians and the civil registry. Late toxicity, occurring and/or persisting after 6 months following treatment, was scored according to CTCAE v4.0 [26]. Only high-grade (equal or higher than grade 3) toxicities were extracted, as these events are clinically most relevant and most reliably extracted retrospectively.

Hyperthermia quality parameters

Hyperthermia treatment characteristics extracted were number of hyperthermia treatments, CEM43T90, TRISE and treatment duration. The CEM43T90 is the mean cumulative equivalent minutes of T90 (temperature reached in at least 90% of measurement locations) at 43 °C [12]. TRISE is a thermal dose parameter based on ALT50 (temperature exceeded by 50% of all measurement sites) and duration of heating. CEM43T90 and TRISE were calculated for all patients, as described previously by our group in detail [27]. Temperatures during treatment were measured intraluminal, but are considered representative for tumor temperatures [28].

Statistical analysis

LC, disease free survival (DFS), DSS and OS were calculated from start date of radiation therapy until the event. LC was noted as 'failed' when a physician diagnosed a local recurrence of cervical carcinoma either clinically or with imaging (CT/MRI). Pathological

confirmation of a recurrence was not required as clinical diagnosis is evident and biopsies are only taken in case of doubt. For DFS, an event was defined as the occurrence of either local or distant recurrence. Patients were censored for local or distant control after the last visit of any physician specifically examining for recurrent disease. For DSS and OS, patients without an event were censored on the day the civil registry was consulted. LC, DFS and DSS were analyzed using the Kaplan–Meier method and statistical differences between groups were determined using the log-rank test. A p-value of $\leq$0.05 was considered statistically significant. Differences in continuous factors between groups were analyzed using the Mann–Whitney U test. Differences in categorical factors between groups were analyzed using the Chi-Square of Fisher's exact test. Hazard ratio (HR) and 95% confidence interval (CI) for various covariates were obtained by univariate Cox proportional hazards analyses. No correction for multiple testing is applied as our primary aim was to validate our previous findings on the 2 thermal dose parameters TRISE and CEM43T90. For categorical values, all categories were compared to the lowest category. Covariates were taken into multivariable analysis based on clinical experience and a p-value $\leq$0.20 in univariate analysis. A backward selection procedure was applied with $p < 0.05$ as a threshold to find the combination of factors that have independent prognostic value. All analyses were performed using IBM SPSS statistics version 24.0 software package (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of the cohort

In total, 227 patients were included in the study. Characteristics of the total cohort are listed in Table 1; detailed information on the distribution over the treatment protocols is provided in the diagram in Fig. 1. Median follow-up time for local and distant recurrence was 52 months (interquartile range (IQR) 30–64 months). Median follow-up time for survival was 82 months (IQR 45–110 months). For the entire cohort, 5-y LC was 72.7%, 5-y DFS was 57.9%, 12-y DSS was 60.0% and 12-y OS was 40.1%. There were 55 cases with a local recurrence out of the 90 cases with any recurrence. Furthermore, there were 74 disease specific deaths out of 107 total deaths. Temperature data were system-lost in 23 cases, hence for thermal dose 204 cases were analyzed.

Table 1
General characteristics of the cohort.

Characteristic	Categories	Value
Patient/tumor characteristics		
Age (years)		Median 54.0 (IQR 43.0–68.8)
Histology	Adeno	26 (11.5%)
	SCC	189 (83.3%)
	Other	12 (5.3%)
FIGO stage	IB	32 (14.1%)
	IIA	10 (4.4%)
	IIB	108 (47.6%)
	IIIA	11 (4.8%)
	IIIB	42 (18.5%)
	IVA	18 (7.9%)
	IVB	6 (2.6%)
Tumor ≥6 cm	No	114 (50.2%)
	Yes	95 (41.9%)
	Unknown	18 (7.9%)
Lymph nodes	Negative	91 (40.1%)
	Iliac	92 (40.5%)
	PAO	43 (18.9%)
	Missing	1 (0.4%)
Induction chemotherapy	No	140 (61.7%)
	Yes	87 (38.3%)
Radiation therapy characteristics		
Radiation technique	3DCRT	135 (59.5%)
	IMRT	50 (22.0%)
	VMAT	42 (18.5%)
Radiation field	Pelvic	169 (74.4%)
	Pelvic + PAO	58 (25.6%)
Brachytherapy use	No	18 (7.9%)
	Yes	208 (91.6%)
	Missing	1 (0.4%)
MRI-guided BT use	No	161 (70.9%)
	Yes	66 (29.1%)
Hyperthermia treatment characteristics		
N of treatments	2	3 (1.3%)
	3	5 (2.2%)
	4	13 (5.7%)
	5	206 (90.7%)
Cumulative TRISE (°C)		Median 3.51 (IQR 3.09–3.91)
	Missing	23 (10.1%)
Cumulative CEM43T90 (min)		Median 3.31 (IQR 1.90–5.54)
	Missing	23 (10.1%)
Treatment duration (min)		Median 89.0 (IQR 88.0–90.0)

Univariate and multivariate Cox proportional hazard analyses

Using univariate Cox proportional hazard analysis, the influence of known prognostic factors and thermal dose on LC, DFS, DSS and OS was analyzed. Histology (squamous cell vs. adenocarcinoma; HR 0.38; 95% CI 0.20–0.74), FIGO stage (IIIA + IIIB vs. IB; HR 3.87; 95% CI 1.45–10.33), CEM43T90 (HR 0.86; 95% CI 0.76–0.98), TRISE (HR 0.54; 95% CI 0.35–0.81) and IGBT (HR 0.46; 95% CI 0.22–0.95) showed a significant effect on LC. FIGO stage and IGBT also had a significant effect on DSS (Table 2). To determine the relative contribution of factors multivariate Cox analyses were performed. As CEM43T90 and TRISE are both indicators of thermal dose, these factors were introduced separately into the analysis. Histology (squamous cell vs. adenocarcinoma; HR 0.33; 95% CI 0.16–0.69), FIGO stage (IIIA + IIIB vs. IB; HR 4.04; 95% CI 1.47–11.14), Lymphadenopathy (negative vs. iliac; HR 2.75; 95% CI 1.37–5.53), TRISE (HR 0.43; 95% CI 0.28–0.68), CEM43T90 (HR 0.83; 95% CI 0.72–0.96) and IGBT (HR 0.40; 95% CI 0.19–0.84) had a significant effect on LC (Table 2). FIGO stage and IGBT also had an independent effect on DSS (Table 2).

The effect of thermal dose in patients treated with modern radiotherapy techniques

A subgroup of 66 patients received state-of-the-art radiotherapy, i.e. Image (MRI) guided brachytherapy (IGBT), and IMRT or VMAT (Fig. 1). These IGBT patients treated with modern radiotherapy techniques, showed a significant higher LC and DSS compared to the non-IGBT patients (Fig. 2). A comparison of other characteristics between the IGBT versus the non-IGBT patients is shown in Supplementary Table A. Next, we explored the effect of thermal dose in the patients treated with modern radiotherapy techniques, which were the 66 patients who had received IGBT (Fig. 1 + 2). There were 9 local recurrences in this patient group. Despite this low number of events, in univariate Cox regression analysis both Histology (HR 0.15; 95% CI 0.04–0.65) and TRISE (HR 0.33; 95% CI 0.12–0.96) remained to have a significant effect on LC (Table 3).

Analysis of grade 3 or higher late toxicity scores in median TRISE and Time Interval groups

To determine the effect of TRISE, CEM43T90 and IGBT use on toxicity, we analyzed the incidence of grade 3 or higher late toxic-

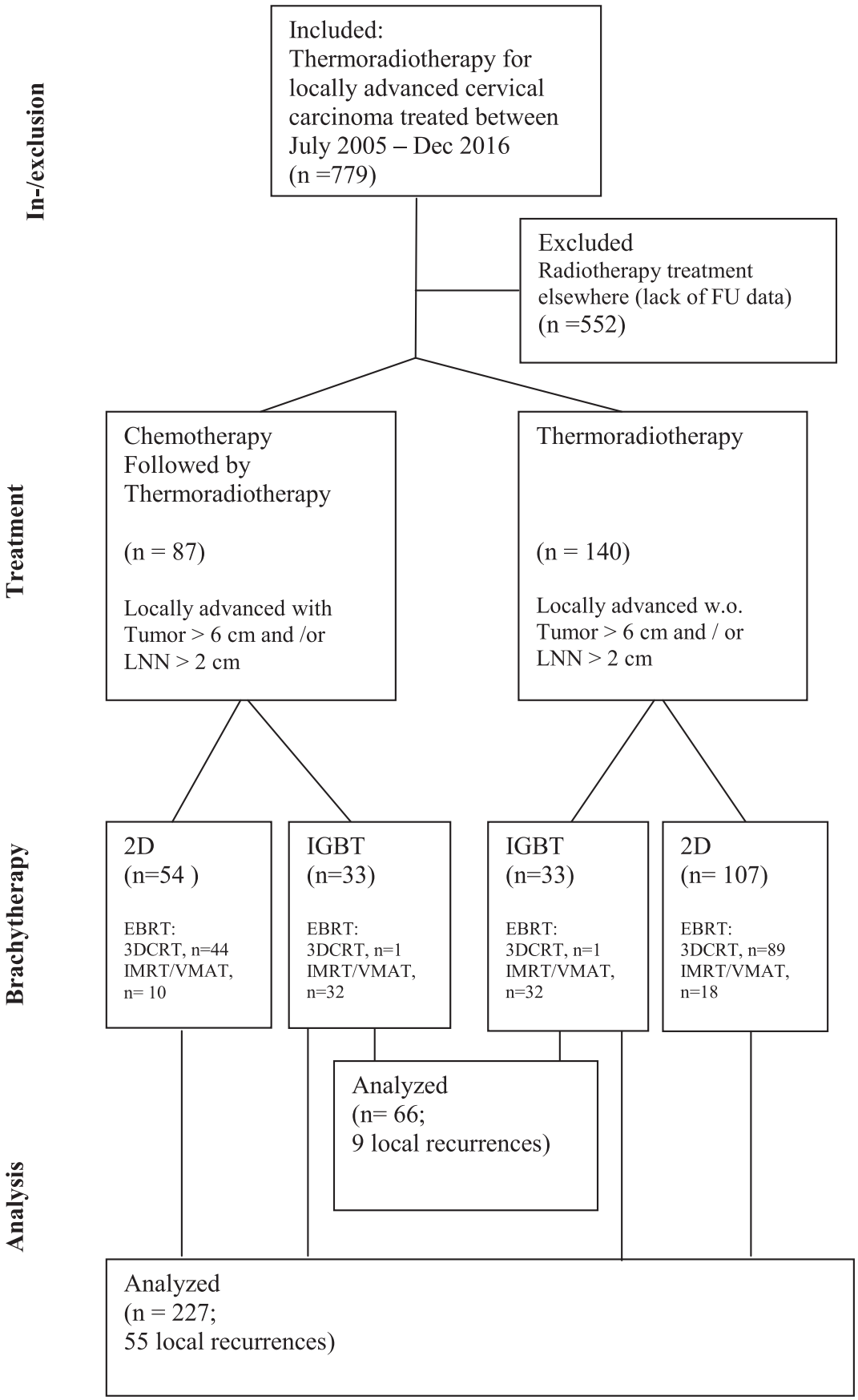

Fig. 1. Consort diagram showing the distribution of patients over treatment protocols and radiotherapy techniques.

Table 2
Univariate and multivariate Cox proportional hazard analyses. Univariate and multivariate Cox proportional hazard regression analysis of factors on LC, DFS, and DSS. Hazard Ratios with corresponding 95% confidence intervals and *p*-values are shown. *In multivariate analysis using CEM43T90, other factors showed similar results compared to results shown here for TRISE.

	Unit variable increase	LC		DFS		DSS	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Univariate analysis							
Age	Years	0.99 (0.97–1.00)	0.107	1.00 (0.99–1.01)	0.944	1.00 (0.99–1.02)	0.765
			0.014		0.007		0.312
Histology	Squamous vs. adeno	0.38 (0.20–0.74)	0.005	0.45 (0.26–0.76)	0.003	0.64 (0.34–1.18)	0.154
	Other vs. adeno	0.71 (0.23–2.24)	0.559	0.81 (0.32–2.05)	0.650	0.89 (0.31–2.51)	0.818
FIGO stage			0.001		<0.001		<0.001
	IIA + IIB vs. IB	1.23 (0.46–3.28)	0.675	1.33 (0.64–2.74)	0.447	1.26 (0.55–2.88)	0.580
	IIIA + IIIB vs. IB	3.87 (1.45–10.33)	0.007	3.34 (1.58–7.06)	0.002	3.54 (1.53–8.19)	0.003
	IVA + IVB vs. IB	2.78 (0.91–8.50)	0.074	2.44 (1.03–5.80)	0.044	3.08 (1.19–7.98)	0.020
Lymphadenopathy			0.076		0.466		0.558
	Iliac vs. negative	2.02 (1.08–3.76)	0.028	1.34 (0.84–2.15)	0.218	1.26 (0.75–2.13)	0.386
	PAO vs. negative	1.30 (0.59–2.90)	0.517	1.16 (0.65–2.07)	0.622	1.35 (0.74–2.50)	0.332
CEM43T90	min	0.86 (0.76–0.98)	0.020	0.95 (0.87–1.04)	0.250	0.98 (0.89–1.07)	0.647
TRISE	°C	0.54 (0.35–0.81)	0.003	0.75 (0.53–1.06)	0.104	0.85 (0.58–1.25)	0.420
IGBT yes/no	Yes vs. no	0.46 (0.22–0.95)	0.036	0.66 (0.39–1.12)	0.122	0.48 (0.24–0.94)	0.033
Multivariate analysis							
			0.009		0.021		
Histology	Squamous vs. adeno	0.33 (0.16–0.69)	0.003	0.46 (0.25–0.84)	0.012		n.s.
	Other vs. adeno	0.75 (0.23–2.45)	0.628	0.89 (0.34–2.36)	0.821		
FIGO stage			0.013		0.003		0.001
	IIA + IIB vs. IB	1.91 (0.68–5.35)	0.218	1.69 (0.76–3.77)	0.200	1.38 (0.57–3.37)	0.477
	IIIA + IIIB vs. IB	4.04 (1.47–11.14)	0.007	3.28 (1.47–7.35)	0.004	3.41 (1.38–8.40)	0.008
	IVA + IVB vs. IB	3.80 (1.20–12.07)	0.024	3.45 (1.36–8.76)	0.009	3.62 (1.33–9.86)	0.012
Lymphadenopathy			0.015				
	Iliac vs. negative	2.75 (1.37–5.53)	0.004				
	PAO vs. negative	1.604 (0.68–3.77)	0.278				
TRISE	°C	0.43 (0.28–0.68)	<0.001	0.70 (0.49–1.01)	0.054		n.s.
IGBT yes/no	Yes vs. no	0.40 (0.19–0.84)	0.016	0.63 (0.37–1.08)	0.094	0.44 (0.22–0.88)	0.020
CEM43T90*	min	0.83 (0.72–0.96)	0.010		n.s.		n.s.

ities. There was no significant difference in the incidence of toxicity in patients with lower or higher than the median TRISE (11.8% versus 10.8%, respectively, $p = 0.825$), lower or higher than the median CEM43T90 (14.7% versus 7.8%, respectively, $p = 0.121$) and patients receiving IGBT or not (7.6% versus 12.4%, respectively, $p = 0.289$) (Table 4).

Discussion

The results of this study confirm the conclusions of our previous cohort study, in which we showed a dose dependent effect of the thermal dose parameters CEM43T90 and TRISE on LC and DSS [11]. In the current, more recent cohort, TRISE and CEMT90 remained to have a significant effect on LC in univariate analysis. An exploratory univariate analysis also showed a significant effect of known predictive factors on LC. In multivariate analysis, TRISE and CEM43T90 had an independent effect on LC. Based upon the results of this study, we conclude that thermal dose is an important parameter to optimize as it is remains predictive for LC in patients treated with state-of-the-art radiotherapy.

Local control (LC) is an essential condition for definitive cure and subsequent patient survival [17]. Other retrospective cohort studies have found similar associations between thermal dose and LC for various tumor types in smaller cohorts [29–34], though some failed to demonstrate such an effect [35]. For this reason, attempts have been made to introduce prospective prescription of thermal dose [36–38]. Jones et al demonstrated that a prescription of >10 CEM43T90 of hyperthermia results in increased LC in patients with varying histology [36]. The most appropriate thermal dose parameter to optimize may depend on tumor type, but is probably more influenced by hyperthermia technique and tumor location. For example, in superficial hyperthermia interstitial ther-

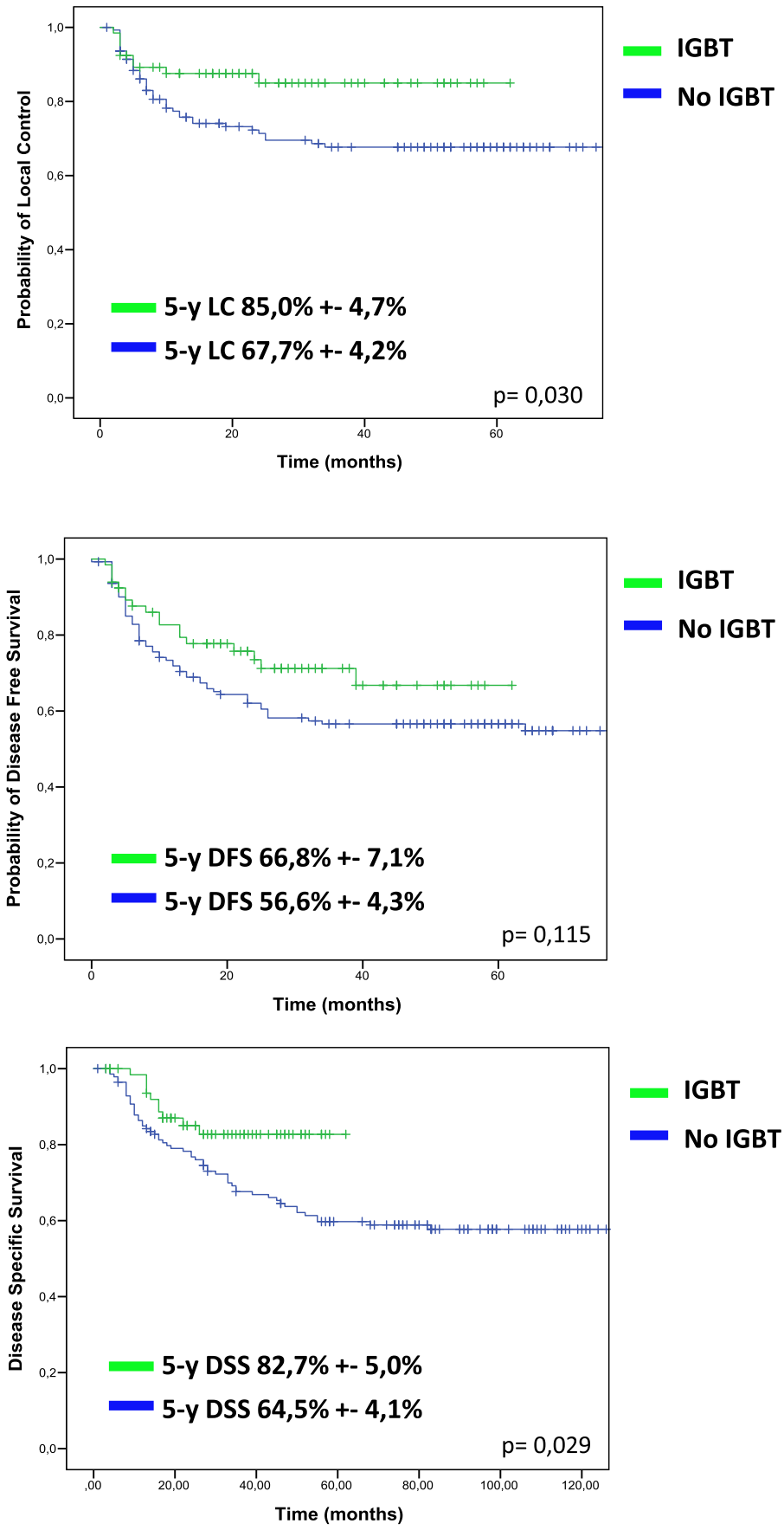

Fig. 2. KM analysis of the effect of the introduction of IGBT. KM curves for LC, DFS and DSS are shown and groups were compared (log-rank test).

Table 3
Univariate Cox proportional hazard analysis in IGBT patients. Univariate Cox proportional hazard regression analysis of factors on LC. Hazard Ratios with corresponding 95% confidence intervals and p-Values are shown.

	Unit variable increase	LC	
		HR (95% CI)	*p*-Value
Histology			0.031
	Squamous vs. adeno	0.15 (0.04–0.65)	0.011
	Other vs. adeno	0.61 (0.06–5.94)	0.674
FIGO stage			0.828
	IIA + IIB vs. IB	0.86 (0.10–7.38)	0.891
	IIIA + IIIB vs. IB	1.713 (0.18–16.51)	0.641
	IVA + IVB vs. IB		0.985
Lymphadenopathy			0.811
	Iliac vs. negative	1.51 (0.30–7.49)	0.618
	PAO vs. negative	0.88 (0.08–9.70)	0.915
CEM43T90	min	0.77 (0.53–1.11)	0.157
TRISE	°C	0.34 (0.12–0.96)	0.042
CTVHR dose	Gray	0.99 (0.91–1.06)	0.707

mometry is the standard, while it is hardly ever possible for deep seated tumors, thereby influencing the most appropriate thermal dose parameter. Moreover, the CEM concept was derived from the impact of thermal dose on direct cell kill and does not necessarily capture the multifactorial effects of hyperthermia [39–41]. As TRISE is more robust, it may capture these multifactorial effects better, at least for deep seated tumors. In the current cohort of cervical carcinoma patients, TRISE remains more predictive for outcome than CEM43T90 (Table 2), but verification for other deep seated tumors is warranted.

Importantly, in patients treated with IGBT, an exploratory analysis showed there was still an effect of TRISE on LC in univariate Cox analysis (Table 3). The relevance of a high thermal dose is further illustrated in an exploratory Kaplan–Meier analysis for the 5-y LC, DFS and DSS in patients with a higher than median TRISE and a higher than median CTVHR (i.e. radiation) dose ($n = 17$) versus patients having a lower than median TRISE and/or a lower than median CTVHR dose ($n = 49$). In the high TRISE/high CTVHR dose patients, the 5-y DFS was 100%, which differed significantly to the DFS in patients with a low TRISE and/or low CTVHR dose (Fig. 3). Although definitive confirmation of a thermal dose effect relationship for state-of-the-art radiotherapy is required in a larger patient population, this finding suggests that hyperthermia also enhances radiotherapy in cervical carcinoma patients treated with a more conformal and higher dose to the tumor area.

Thermal dose has also been associated with increased late toxicity, for example skin damage in a retrospective cohort study of 262 recurrent breast cancers [42]. In our cohort, we did not observe differences in late severe toxicity between high or low thermal dose groups. Also, the introduction of IGBT did not significantly increase late toxicity. These results of our current study are in line with the results from the Dutch Deep Hyperthermia trial and our previous cohort, both demonstrating no added late toxicity of deep hyperthermia in the pelvic region [3,6,8,11]. Similarly, others have found that the use of IGBT has not resulted in higher late toxicity rates [17,43].

The confirmation of a thermal dose effect on clinical outcome suggests that further enhancement of the quality of the hyperthermia treatment potentially leads to further clinical improvement. A higher thermal dose can be achieved through an increase in temperature (i.e. improved spatial control of the energy deposition), longer treatment times or addition of hyperthermia treatments. By use of hyperthermia planning we aimed to increase temperatures in the target area [21]. MRI-guided hyperthermia could potentially lead to higher temperatures in the target areas in the future. MRI is a useful tool to improve the optimization algorithm by improved understanding of hotspot development and aid of applicator design [44]. Finally, another approach is to better exploit the biological mechanisms of hyperthermia using novel sensitizers [40,45].

Comparing the outcome results of the current cohort to previous results, the 5-year LC in our current cohort was 72.7%, compared to 61.0% in the thermoradiotherapy arm of the Dutch Deep Hyperthermia Trial and to 53.0% in our previous cohort [3,11]. The 5-year DSS in the current cohort was also higher, i.e. 62.9%, compared to 47.0% in our previous cohort of cervical cancer patients [11]. These marked differences between our current cohort and the previous cohort in LC and DSS can be explained by improvements in radiotherapy techniques. Additionally, improvements in hyperthermia delivery and quality, may also contribute to the improved outcomes observed. All of these factors may play a role, but a clear benefit of IGBT has been demonstrated in literature in terms of improved LC and OS [15–18].

In conclusion, this study confirms our earlier reported relationship between thermal dose and clinical outcome in patients with cervical cancer, also in patients treated with modern radiotherapy

Table 4
Analysis of Grade 3 or higher late toxicity. Incidence of grade 3 or higher late toxicity in various patient groups was analyzed. *p*-Values are shown.

	Low TRISE	High TRISE	*p*-Value
			0.825
No grade 3 or higher toxicity	91 (89.2%)	90 (88.2%)	
Grade 3 or higher toxicity	11 (10.8%)	12 (11.8%)	
Total	102 (100%)	102 (100%)	
	Low CEM43T90	High CEM43T90	*p*-Value
			0.121
No grade 3 or higher toxicity	94 (92.2%)	87 (85.3%)	
Grade 3 or higher toxicity	8 (7.8%)	15 (14.7%)	
Total	102 (100%)	102 (100%)	
	No IGBT	IGBT	*p*-Value
			0.289
No grade 3 or higher toxicity	141 (87.6%)	61 (92.4%)	
Grade 3 or higher toxicity	20 (12.4%)	5 (7.6%)	
Total	161 (100%)	66 (100%)	

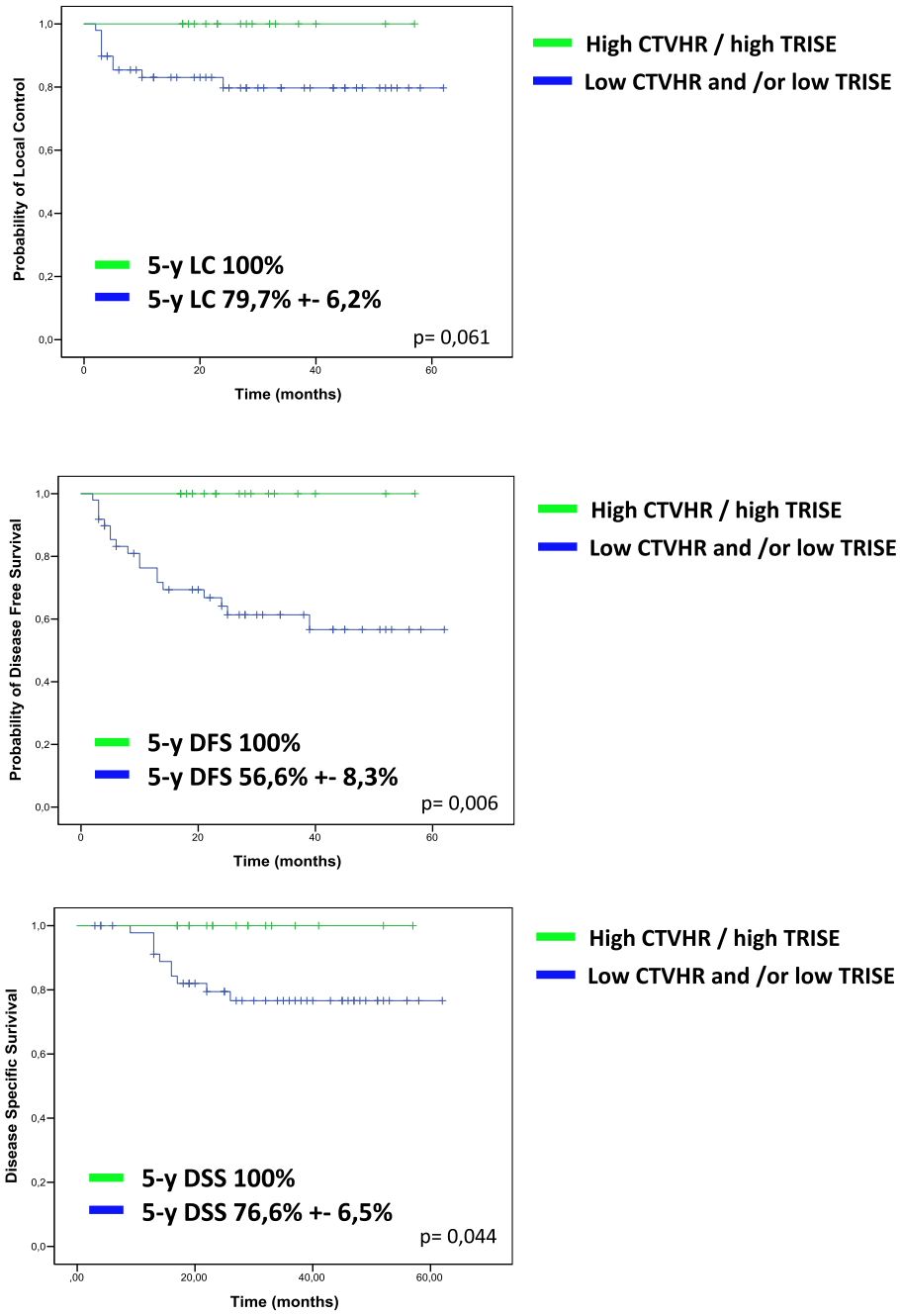

Fig. 3. KM analysis of the combined effect of thermal and radiotherapy dose in patients treated with IGBT. KM curves for LC, DFS and DSS are shown and groups were compared (log-rank test).

techniques. This is a strong encouragement to continue our efforts to improve the quality of the hyperthermia treatment as this effort could translate directly into improved clinical outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.021.

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