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Original Article

Hyperthermia with radiotherapy reduces tumour alpha/beta: Insights from trials of thermoradiotherapy vs radiotherapy alone

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ABSTRACT

Purpose: Hyperthermia inhibits the repair of irradiation-induced DNA damage and thereby could alter the α/β values of tumours. This study estimates the clinical α/β_{HTRT} values from clinical trials of thermoradiotherapy (HTRT) vs radiotherapy (RT) in recurrent breast (RcBC), head and neck (III/IV) (LAHNC) and cervix cancers (IIB-IVA) (LACC).

Methods: Three recently published meta-analyses for HTRT vs RT in RcBC, LAHNC and LACC were evaluated for complete response (CR). Studies with specified RT dose (D), dose/fraction (d) and corresponding CRs were selected. Tumour biological effective dose (BED) for each study with RT (BED_{RT}) was computed assuming an α/β_{RT} of 10 Gy. As outcomes were favourable with HTRT, thermoradiobiological BED (BED_{HTRT}) was calculated as a product of BED_{RT} and $\%CR_{HTRT}/\%CR_{RT}$. The α/β_{HTRT} was estimated as $Dd/(BED_{HTRT} - D)$.

Results: 12 trials with 864 patients were shortlisted – RcBC (3 studies, $n = 259$), LAHNC (5 studies, $n = 338$) and LACC (4 studies, $n = 267$). Overall risk difference of 0.28 favoured HTRT ($p < 0.001$). Mean BED_{RT} and BED_{HTRT} were 64.7 Gy (SD: ±15.5) and 109.5 Gy (SD: ±32.1) respectively and global α/β_{HTRT} was 2.25 Gy (SD: ±0.79). Mean α/β_{HTRT} for RcBC, LAHNC and LACC were 2.05 Gy, 1.74 Gy and 3.03 Gy respectively. On meta-regression, α/β_{HTRT} was the sole predictor for the corresponding risk differences of the studies (coefficient = −0.096; $p = 0.03$).

Conclusion: Thermoradiobiological effects on the repair of RT induced DNA damage results in reduction in α/β values of tumours. This should be considered to effectively optimize HTRT dose-fractionation schedules in the clinic.

Hyperthermia (HT), as defined by the Kadota Fund International Forum in 2004, is the elevation of loco-regional tumour temperature to a range between 39 and 45 °C [1]. At these modest temperatures, HT exhibits a potent radiosensitizing effect [2–4] and also interacts favourably with numerous chemotherapy (CT) agents. Importantly, it supplements the immunomodulatory effects of radiotherapy (RT), akin to "*in situ* tumour vaccination" [5–9]. Thus, HT is a unique modality with multifaceted actions, the use of which has translated into positive therapeutic gains in several randomized clinical trials and meta-analyses with RT and/or CT in different tumour sites [10–17].

HT-induced radiosensitization has been primarily attributed to its influence on the hypoxic tumour cells and its ability to inhibit the repair of the RT-induced DNA damage [5,18,19]. HT sensitizes the radioresistant hypoxic cells by improving oxygen delivery at temperatures between 40.5 °C and 42.5 °C [19]. The action of HT on DNA repair is reported at multiple points in the mechanisms [18]. RT-induced DNA damage, namely base damage and single and double strand breaks can result in sublethal, potentially lethal or lethal damage depending on the DNA repair mechanisms [20]. HT is known to inhibit the repair of such DNA damage by inactivating various DNA repair enzymes of these repair pathways [18,21]. Even though the exact mechanisms of inhibition of HT-induced DNA repair have not yet been fully elucidated, multiple pathways result in enhancing RT-induced cell kill and thermoradiosensitization. These radiobiological attributes of HT share considerable similarity with those of high linear energy transfer radiation, e.g. ^{12}C ion therapy [22].

Abbreviations: BED, biological effective dose; BED_{HTRT}, biological effective dose with thermoradiotherapy; BED_{RT}, biological effective dose with radiotherapy alone; CR, complete response; D, total radiotherapy dose; d, radiotherapy dose per fraction; HTRT, thermoradiotherapy; LACC, locally advanced cancer cervix; LAHNC, locally advanced head and neck cancer; L-Q, linear-quadratic; n, number of fractions; ns, not significant; OR, odds ratio; RcBC, recurrent breast cancer; RD, risk difference; RR, risk ratio; RT, radiotherapy; α/β_{HTRT}, tumour α/β values with thermoradiotherapy; α/β_{RT}, tumour α/β values with radiotherapy alone.

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The linear-quadratic (L-Q) model is based on the ratio of the linear and quadratic components of cell kill. The sensitivity to fraction size summarized by the α/β value (where the linear and quadratic components are equal) has been widely used to design RT dose fraction schedules in clinical practice. The linear component α determines the initial slope of the cell survival curve and the effect of single ionization events at low RT doses whilst β, the quadratic component, represents the cell survival after two or more chromosomal lesions [23]. Data from various tumours indicate that α/β values with RT (α/β_{RT}) could vary from ~4 Gy to ~10 Gy depending on the high or low fractionation sensitivity of the tumours respectively [24–26].

In clinical practice, RT dose-fractionation schedules are usually based on the L-Q model. Even though this mechanistic model empirically fits the complex interactions of ionizing radiation at the molecular and cellular levels, it is ubiquitous due to its simplistic approach using few parameters and has been validated both in *in vitro* and *in vivo* conditions over a specified dose per fraction range [27].

Various mechanisms have been proposed for the linear (α) and quadratic (β) DNA damages in the L-Q model. Most of the cell kill is attributed to α inactivation which, in contrast to β inactivation, is not repairable [28]. It would be prudent to note that the estimates of α/β in *in vitro* conditions are of cell populations with homogenous radiosensitivity due to the presence of synchronized cells. Furthermore, the high dose rates and optimum controlled conditions inhibit DNA repair enzymes and could thereby minimize the repair of sublethal or potentially lethal RT damage [28]. As the clinical situation is far from that created in the laboratory, α/β estimates from clinical data of the same tumour type have shown wide variation. This is partly attributed to the clinical and methodological factors used for these estimations [20,24]. Nonetheless, a generic α/β value of 10 Gy has usually been assumed for most tumour types for various radiobiological computations including BED [25,26,29,30].

The linear component of cell kill, α, being non-repairable, contributes to the majority of the cell kill. Unlike the steeper cell survival curves of oxic (aerobic) cell lines, the cell survival curves of hypoxic cells usually have a wider shoulder indicating a lower α component of cell kill [19,31]. *In vitro,* HT can moderately enhance the α component [32,33]. In the clinic, the HT-induced oxygenation of radioresistant hypoxic tumour tissue could achieve radiosensitization, analogous to the enhancement of α observed *in vitro*.

In contrast to the α component of cell kill, the quadratic (β) component contributes to a small proportion of RT cell kill as most of the base damage and single strand DNA breaks are repairable. However the β contribution could increase if the DNA repair pathways were to be inhibited [20]. Using cell survival studies with SiHa cell lines, Franken et al. [33] reported that at 41 °C, the α/β reduced from 13.8 to 3.3 Gy. HT at both 41 °C and 43 °C was shown to enhance the β by 3.9 and 2.7 times respectively. This resulted in a reduction in the α/β ratio by nearly 76% (from 13.8 to 3.3 Gy) at 41 °C and by 37% (from 13.8 to 8.7 Gy) at 43 °C. The reduction at 41 °C was reported to be primarily due to an increase in β, whilst at 43 °C, both components showed an increase, β more so than α.

The enhancement of the quadratic component of cell kill from the addition of HT to RT could result from the inactivation of DNA repair enzymes, an increase in chromosomal aberrations, increased induction of apoptosis and breakdown of BRCA2, a protein of the homologous recombination DNA repair pathway [32–34]. All of these would result in a reduced α/β value due to the overwhelming enhancement of β by HTRT.

To further assess whether such a correlation could be evident clinically with thermoradiotherapy (HTRT), α/β values following HTRT (α/β_{HTRT}) were estimated in recurrent breast cancers (RcBC) [35,36], locally advanced head and neck cancers (stages III/IV) (LAHNC) [37–41] and locally advanced cancer cervix (stages IIB–IVA) (LACC) [42–45] based on data from clinical trials between HTRT and RT.

Materials and methods

Study selection

Clinical trials comparing HTRT against RT in patients diagnosed with RcBC, LAHNC and LACC were considered for this study. Three recently reported meta-analyses published in 2016 for each of these tumour sites were screened [14–16]. In addition, a PubMed search using the Medical Subject Headings (MeSH) terms "Hyperthermia, Induced", "Clinical Trial", "Radiotherapy" was conducted to check for any additional relevant trials that might have been reported up to the date of the last search on February 8, 2019. The inclusion criteria were studies in which (a) majority of patients were treated with the specified RT dose and dose per fraction and (b) complete response rate (CR) at end of treatment was reported. Studies which treated patients with different RT doses or dose per fraction and whose corresponding CRs were not reported for each fractionation schedule were not included in this study.

Estimation of biological effective dose (BED) and α/β with or without hyperthermia

The tumour BED for each study was computed using the L-Q model without a time factor correction as [29]:

$$BED = nd\ [1 + d/(\alpha/\beta)] \quad (1)$$

where, *n* represents the number of fractions and *d* the dose/fraction. An α/β of 10 Gy has been assumed for RcBC, LAHNC and LACC in this computation [24,29]. For treatments with RT alone, the BED is indicated as BED_{RT}. As the dose-fractionation parameters for both HTRT and RT groups of each trial were identical, the better CRs observed uniformly across all trials with HTRT could be attributed to a higher BED resulting from the addition of HT to RT. Thus, the effective BED for HTRT (BED_{HTRT}) was computed as:

$$BED_{HTRT} = BED_{RT} \times (\%\,\text{Complete response with HTRT} / \%\,\text{Complete response with RT}) \quad (2)$$

As the *n* and *d* were the same for both HTRT and RT schedules, the only factor underlying the increased BED_{HTRT} could be a difference in α/β value, due to addition of HT to RT, denoted as α/β_{HTRT}. This was computed as:

$$BED_{HTRT} = nd\ (1 + d/\alpha/\beta_{HTRT}) = D\ (1 + d/\alpha/\beta_{HTRT}) \quad (3)$$

As *D*, the total RT dose, = nd,

$$\alpha/\beta_{HTRT} = Dd/(BED_{HTRT} - D) \quad (4)$$

The α/β_{HTRT} was thus estimated separately for each of the trials in RcBC, LAHNC and LACC.

Computation of the effect measures and meta-regression for complete response

The effect measures – odds ratio (OR), risk ratio (RR) and risk difference (RD) for CR between HTRT and RT were computed using the Comprehensive Meta-analysis Software package (version 3.0) [46]. A random effects model was used and the results given by the point estimate, the 95% confidence interval (CI), Z and p value. Heterogeneity was assessed using the I^2 statistic, which represents the estimated proportion of unexplained inter-study variance prior to pooling of the studies. An I^2 of ≤40% was interpreted as the absence of any substantial heterogeneity [47]. Potential publica-

tion bias was evaluated through funnel plots and rank correlation tests with Kendall's tau [48].

Subgroup analyses were performed to look for the impact of the three different tumour sites on the risk difference. The Q value, degree of freedom and p value were computed. Meta-regression was undertaken to evaluate the relationship of the covariates and the RD. Intercept was used in the meta-regression model. All p-values are two-sided and considered statistically significant if $\leq$0.05.

Results

Overview of the shortlisted clinical trials

Based on our inclusion criteria, only 12 of the 18 trials included in the three meta-analyses [14–16] could be considered for this study [35–45]. Six trials were excluded as the patients in both groups received varying RT dose fractionation schedules. No additional studies were discovered through the updated search. Thus 12 trials of which two were nonrandomized [35,41] totalling 864 patients were included in this analysis. 454 patients received HTRT whilst 410 were treated with RT. The summary of the RT dose, RT dose per fraction, temperatures attained, duration of treatment, number of HT sessions per week and total number of HT sessions are given in Table 1. Locoregional superficial HT was used for RcBC and LAHNC whilst deep HT was used in LACC. The number of HT sessions varied between 1 and 3 per week (mean ± SD: 1.7 ± 0.6) whilst the total number of HT sessions delivered ranged from 3 to 12 (mean ± SD: 7.5 ± 3.3). In nine studies, RT was followed by HT whilst in two, HT was delivered before RT. In one study, the sequence of HT and RT was not stated. The mean ± SD temperatures for RcBC, LAHNC, LABC were 43.0 ± 0.0 °C, 42.8 ± 0.8 °C and 41.7 ± 0.9 °C and was nonsignificant (ANOVA, $F = 2.502$, $p = 0.143$).

CR was achieved in 43.1% (177/410) with RT compared to 69.8% (317/454) with HTRT (RD: 0.28, 95% CI 0.22–0.34, $p < 0.001$, Fig. 1). Likewise, the OR and RR were both in favour of HTRT (OR: 3.33, 95% CI 2.48–4.46, $p < 0.001$; RR: 1.61, 95% CI 1.43–1.82, $p < 0.001$). No publication bias was evident (Kendall's tau: 0.075, p: ns) (Fig. 2). On subgroup analysis, the differences in RD between the three tumour sites were not significant ($Q = 1.72$, $I^2 = 0.00$, p: ns) (Fig. 1).

Three of 12 studies (259 patients) were in loco-regional RcBC [35,36]. 106 patients received RT whilst 153 were treated with HTRT. RT to both arms ranged between 28.8 Gy and 48 Gy (mean ± SD: 36.3 ± 10.3 Gy) and was delivered at a dose per fraction of 2 to 4 Gy (3.2 ± 1.0 Gy). Patients in the HTRT group received 60 min of once or twice weekly HT to a temperature of 43 °C for 3 to 8 sessions (median: 5.5) (Table 1). The CR rate at end of treatment was reported as 33% with RT, compared to 62.7% with HTRT (RD = 0.31, 95% CI: 0.19–0.42, $p < 0.001$) (Table 1, Fig. 1).

Five studies (338 patient) in LAHNC received 60 to 70 Gy (66.4 ± 4.3 Gy) at 1.5 to 2 Gy (1.9 ± 0.2 Gy) per fraction [37–41]. Six to 12 HT sessions (median: 7.0) were usually delivered twice weekly (range 1–3). A mean temperature of 42.8 °C was attained (range: 42.3–44.4 °C). CR with HTRT and RT were 71.6% and 41.2% respectively (RD = 0.31, 95% CI: 0.21–0.41, $p < 0.001$) (Table 1, Fig. 1).

In four studies in LACC, 267 patients were randomized to receive HTRT ($n = 135$) or RT ($n = 132$) [42–45]. The mean external RT dose was 50.1 Gy (range: 40–60 Gy) and delivered at a mean dose per fraction of 1.95 Gy (range: 1.8–2 Gy). A mean temperature of 41.7 °C (range: 40.6–42.5 °C) was attained during the 3 to 12 HT sessions (median: 6.5) delivered once or twice a week over 45–60 min (mean: 52.5 min) (Table 1). 75.5% achieved CR with HTRT in contrast to 53.7% with RT (RD = 0.22, 95% CI: 0.11–0.33, $p < 0.001$) (Table 1, Fig. 1).

Biological equivalent dose and α/β_{HTRT}

The BED_{RT} varied in the 12 studies between 39.2 and 84.0 Gy depending on the individual total RT dose and dose/fraction used in these studies. The mean BED_{RT} was 64.7 Gy_{10} (±SD: 15.6). For each tumour site, the mean BED (±SD) for RcBC, LAHNC and LACC were 47.2 Gy_{10} (±9.4) (3 studies), 79.1 Gy_{10} (±6.3) (5 studies) and 59.9 Gy_{10} (±9.9) (4 studies). The BED_{HTRT} computed for each study using the BED_{RT} and ratio of the %complete response in HTRT vs RT groups (equation (2)) ranged between 61.7 Gy and 165 Gy (mean ± SD: 109.5 Gy ± 32.1). Correspondingly, the estimated α/β_{HTRT} varied from 1.28 to 3.70 Gy (2.25 ± 0.79, 95% CI: 1.80–2.70) (Table 1).

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

Abbreviations: RT: Radiotherapy; HTRT: Thermoradiotherapy; T: Temperature; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; BED: Biologically effective dose; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; $\%CR_{HTRT}$: % complete response with HTRT; $\%CR_{RT}$: % complete response with RT.
BED_{HTRT} and α/β_{HTRT} are estimated as described in text.
*Average dose to RT group: 68 Gy whilst to HTRT 67.5 Gy.
+Only patients with neck nodes were considered, treated with 1.5 Gy–2 Gy per fraction, 3 fractions/day.
For all LACC studies, only external RT doses were considered.

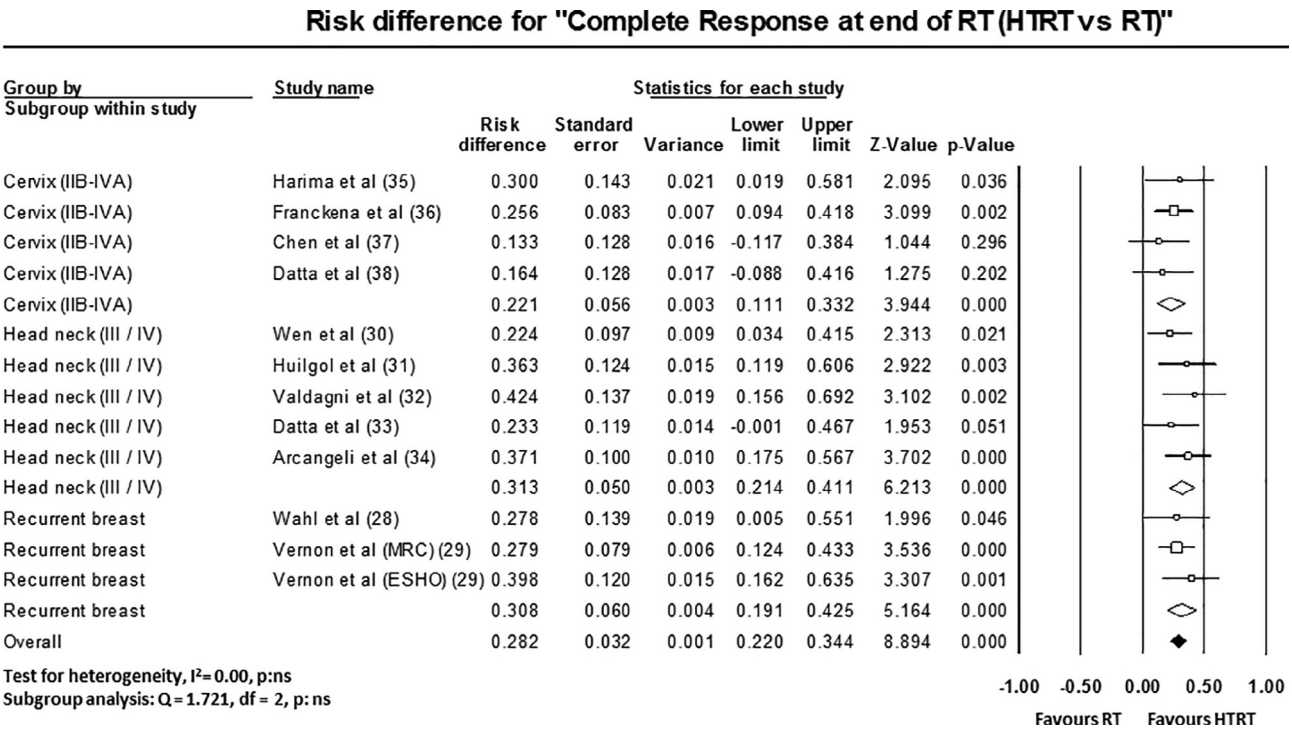

Fig. 1. Forest plots for the risk difference between radiotherapy (RT) vs thermoradiotherapy (HTRT) studies in locally advanced cancer cervix, locally advanced head & neck cancer and recurrent breast cancer.

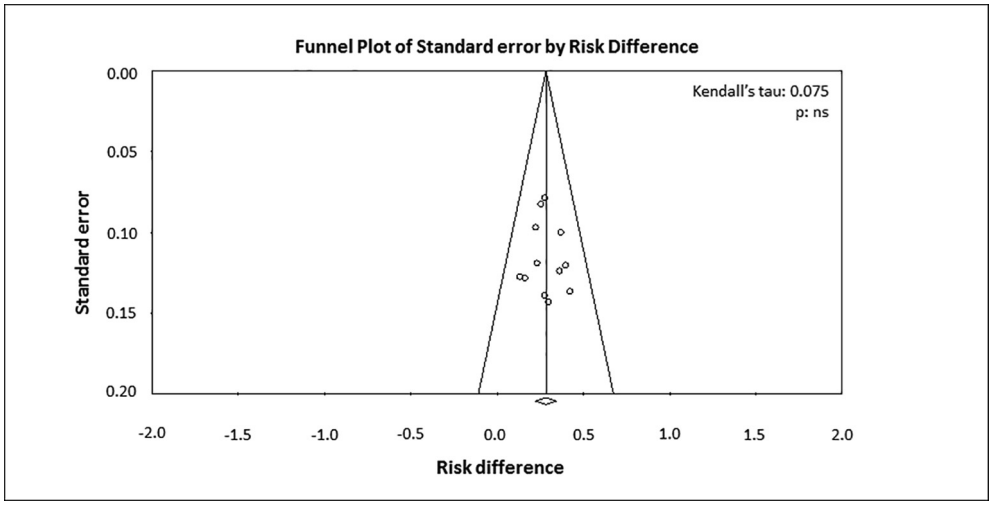

Fig. 2. Funnel plot along with Kendall's tau and p value for the risk difference for the clinical trials with radiotherapy (RT) vs thermoradiotherapy (HTRT).

For RcBC, the mean effective BED_{HTRT} was 89.2 Gy (range: 77.0–98.7) compared with 47.2 Gy_{10} for RT (range: 39.2–57.6). The α/β_{HTRT} varied from 1.89 to 2.15 (mean: 2.05, 95% CI: 1.90–2.22). The mean effective BED_{HTRT} for LAHNC was 141.9 Gy (range: 124.2–165.0) compared with 79.1 Gy_{10} (range: 69–84). Thus the computed α/β_{HTRT} varied between 1.28 and 2.58 Gy (mean: 1.74, 95% CI: 1.29–2.19) (Table 1). For LACC, the mean effective BED_{HTRT} was 84.2 Gy (range: 61.7–98.5) vs 59.9 Gy_{10} (range: 48–72) with RT alone. Correspondingly the computed α/β_{HTRT} varied between 2.03 and 3.70 Gy (mean: 3.03, 95% CI: 2.24–3.82) (Table 1).

On an independent sample "t test", the significant difference in α/β_{HTRT} was evident for LAHNC vs LACC ($p = 0.041$). The α/β_{HTRT} for the three tumour sites were significantly different (ANOVA, $F = 5.579$, df = 11, $p = 0.027$). On meta-regression, only the computed α/β_{HTRT} predicted for RD and showed an inverse relation (coefficient: −0.096, $p = 0.037$) (Fig. 3). None of the other RT and HT parameters were found to be significant on meta-regression for RD.

Discussion

Radiation therapy treatment protocols are often dictated by the radiation sensitivity (α/β) of the tumour to fraction size in relation to the adjacent normal structures. It would therefore be of considerable interest to investigate any changes in α/β due to added therapeutic interventions such as hyperthermia, which is known to be one of the most potent radiosensitizers [4].

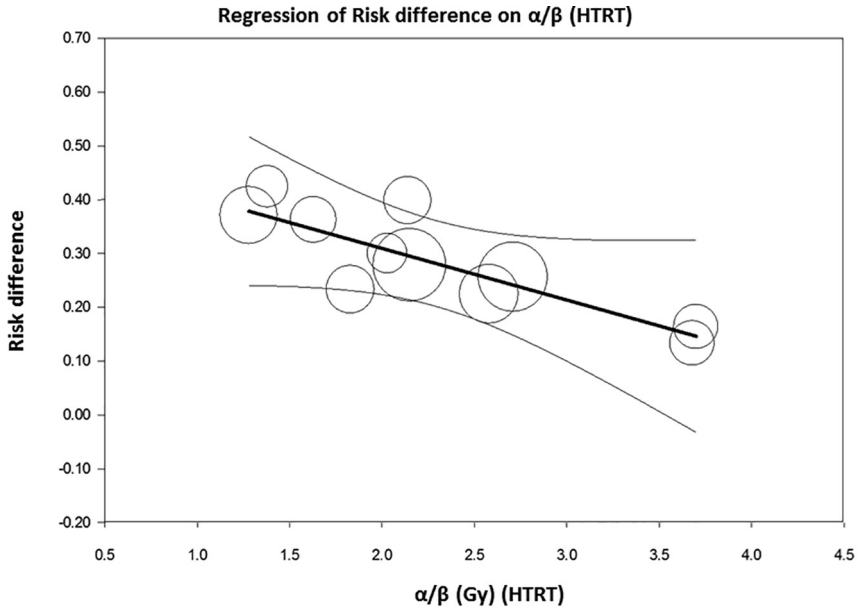

Fig. 3. Regression plots for risk difference using random-effects model for the estimated α/β values for thermoradiotherapy (HTRT) (coefficient = −0.096; $p = 0.03$). Each study is shown as a circle and the size of the circle is proportional to the study's weight in the analysis. The central bold line indicates the regression line whilst the upper and the lower lines indicate the respective 95% confidence interval limits.

The direct thermophysiological effects of local hyperthermia in tumour and normal tissues (perfusion, oxygenation, blood flow) are usually transient but could indirectly influence the thermal radiosensitization through reoxygenation. However, DNA damage by inhibition of DNA repair could be expected to be more robust as this is reflected by a markedly higher β component of cell kill in contrast to the alteration in the α component [33]. This is evident from the *in vitro* experiments which show a fall in α/β_{HTRT} after just 1 hour of heating. Thermophysiological modifications in tissues cannot be attributed to this alteration in α/β. All the effects observed with HTRT could therefore be primarily due to the interference of HT with DNA repair pathways.

The 12 studies provided an opportunity to estimate the clinical α/β values in patients receiving HTRT. As all studies showed an improved CR rate with HTRT, it was logical to assume that the enhancement in clinical outcome was the result of a higher BED in tumours treated with HTRT as the RT doses were identical in both groups. This allowed us to estimate the α/β_{HTRT} and the values derived corresponded well with the *in vitro* studies [33] (Fig. 4).

In the clinical setting, heterogeneity in the temperature distribution within the tumour and normal tissues is expected. The normal tissues are spared from thermal radiosensitization by physiological vasodilation and consequent 'washing out' of heat, a phenomenon similar to the "heat sink" effect. This is corroborated by clinical studies of HTRT where neither acute nor late morbidities were significantly augmented by addition of HT to RT in most series [5,14,15,49,50]. Tumours are known to have complex and chaotic vascular arrangements, supplemented by raised interstitial pressure due to high tumour cell density [51]. Thus, applied heat could be differentially trapped resulting in heterogeneity of temperature. This could result in differential thermal enhancement of α and β components as observed in *in vitro* experiments [33] and lower the overall tumour α/β with HTRT as evident in this study.

The present estimates are based on a minimum data set of RT dose parameters available in only 12 studies. Six additional studies, in which a significant proportion of patients received varying RT doses and/or fractionation, could not be included as the analysis of individual patient data was beyond the scope of this study. In addition, to safeguard against the introduction of any assumptions for radiobiological parameters in our BED estimations, the time factor was omitted for both groups. Similarly in LACC, only the external RT dose was considered and no attempt was made to convert and add the various dose-rates of brachytherapy. This has been adhered to uniformly for all studies.

The difference in α/β_{HTRT} between the 3 sites was shown to be significantly different on ANOVA ($p = 0.027$). On an independent sample t test to check which individual groups contributed to this difference in α/β_{HTRT}, it was evident that α/β_{HTRT} varied only between LAHNC and LACC ($p = 0.04$) and not between LAHNC and RcBC or RcBC and LACC. Although the exact reason for this is not very apparent, it could be a function of sample size as only 3 studies (total patients = 259) were included in RcBC whilst LAHNC and LACC had 5 (total patients = 338) and 4 (total patients = 267) studies respectively. However, it was more important to see which predictive variables influenced α/β_{HTRT}. A meta-regression was therefore carried out to identify the significant predictive variable(s). This revealed that α/β_{HTRT} was significantly and solely influenced by the risk difference between HTRT and RT, which showed an inverse correlation (coeff: −0.096, $p = 0.037$) (Fig. 3).

The results of this study have some inherent limitations as the estimates have been carried out using summary data and not individual patient data. These include that (a) the thermal dose relationship could not be ascertained from the summary data as this would require the temperature profiles vs time for each individual patient; (b) a considerable variability was evident in the sequencing of HT and RT in these 12 studies (Table 1). Furthermore, the interval between HT and RT was also variable or was not uniformly reported in these studies. The time intervals were not reported in 5 of the 12 studies whilst in others it varied between immediately and 60 mins. Thus, no conclusion could be drawn regarding the impact of time interval between HT and RT on the outcomes and α/β_{HTRT}. Nevertheless, we acknowledge the importance of the time interval between the two treatments and it is often recommended that this should be kept to a minimum. However two contradictory studies on this issue have been recently reported in LACC. Whilst van Leeuwen et al. [52] reported that in 58 LACC patients, a short

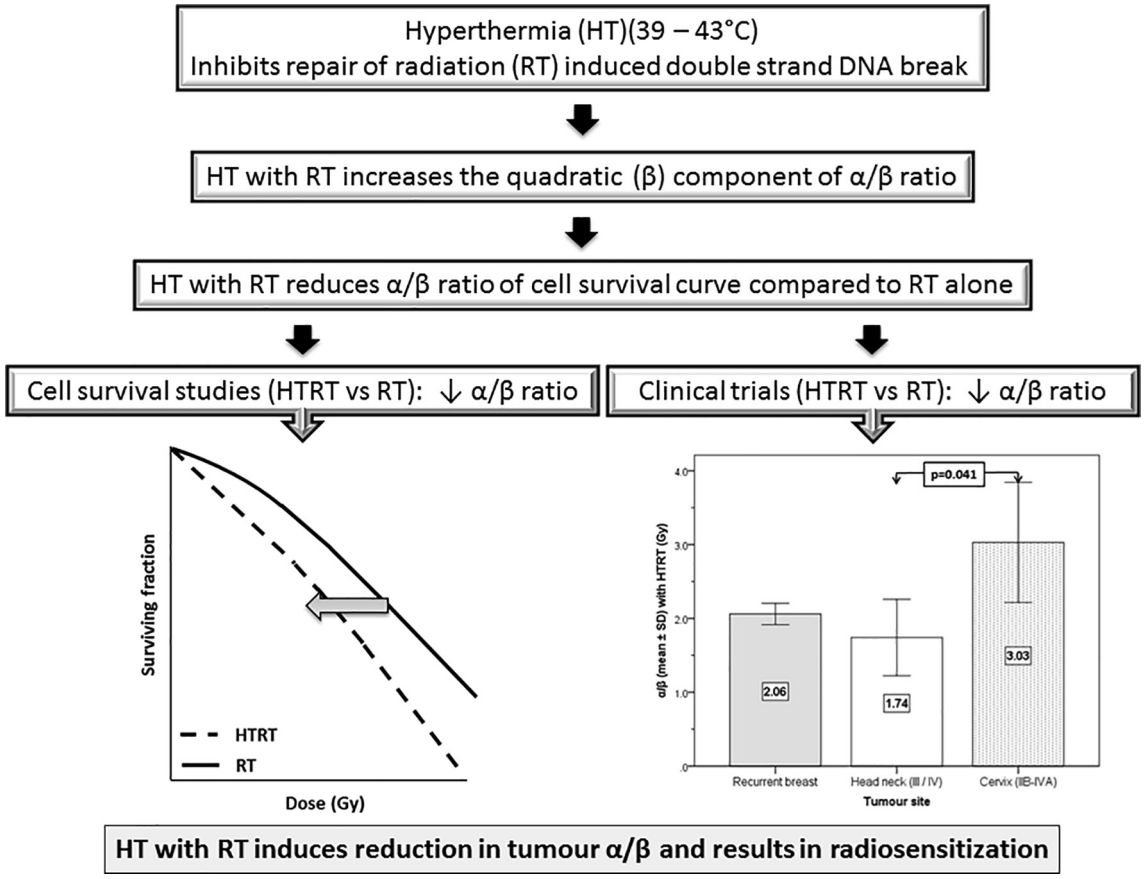

Fig. 4. Hyperthermia results in reduction in α/β values. This was evident in cell survival studies reported by Franken et al. [33] and corroborates the estimated α/β values from clinical trials of radiotherapy (RT) vs thermoradiotherapy (HTRT) in recurrent breast cancers, locally advanced head & neck cancer and locally advanced cancer cervix in the present study.

time interval between RT and HT reduced in field recurrences; Kroesen et al. [53] showed that a time interval between RT and HT of up to 4 hours had no effect on clinical outcome in 400 LACC patients. Thus it is evident that the optimum time interval between HT and RT remains under debate.

A prospective randomized trial is therefore required with accurate volumetric temperature distribution in tumour and adjoining normal tissue. This should enable comparison of the duration of hyperthermia, the time interval between HT and RT and the sequencing of HT and RT. All of these are necessary to address the key thermoradiobiological issues with reasonable certainty and could also help to quantify the α/β_{HTRT} in each individual case. This is beyond the scope of this manuscript; however the findings of this study should encourage the planning of such a prospective well-designed study to optimize the clinical practice of HTRT.

The implications of a reduction in α/β with HTRT could be considered whilst designing RT schedules with HT. The lowering of α/β with HTRT could justify hypofractionated regimens. This could be useful as HT is usually performed one or twice weekly in most centres. The hypofractionated RT schedules could be combined with HT sessions to gain the maximum thermoradiosensitization effect. As there is a general trend towards practising hypofractionated regimes [54], such schedules may not be out of place, especially in palliative situations like RcBC. Hypofractionation has been effectively practised in the palliation of RcBCs with HTRT using RT doses ranging from 1.8 to 4 Gy/fraction (2.8 ± 0.9) [14]. Similarly a higher RT dose per fraction with HT in elderly patients with muscle invasive bladder cancer enhanced the BED_{HTRT} and subsequently tumour control without any significant detrimental effects on acute and late morbidities [49].

In curative situations, such as LAHNC or LACC, if hypofractionation is not feasible due to the potential risk of increased normal tissue morbidity, one could use HT along with simultaneous integrated boost intensity modulated radiotherapy, to selectively deliver a higher RT dose per fraction to the gross tumour. Palliative RT schedules in RcBC are usually delivered with relatively higher dose/fraction. With regard to brachytherapy, most centres currently practice high-dose-rate brachytherapy which usually delivers a higher dose/fraction.

Presently, efforts are underway to develop integrated HTRT treatment planning systems to model the biological effectiveness of HTRT [5,55,56]. Correct mathematical models with valid thermoradiobiological parameters to compute the BED_{HTRT}, are therefore mandatory. The reduction in α/β with HTRT and the resultant increased BED_{HTRT}, as estimated in this study, could assist in truly representing the effectiveness of HTRT in integrated treatment planning systems. However, as in RT treatment plans, the heterogeneity in temperature distributions in tumours and normal tissue during clinical HT delivery and its impact on the alteration in α/β_{HTRT} needs to be taken into account in integrated HTRT treatment planning systems. This might even require a volumetric temperature profile mapping within the heated volume akin to radiation dose distribution in the irradiated volume.

In conclusion, HT added to RT achieves a significant reduction in α/β value, as estimated clinically in RcBC, LAHNC and LACC. This is congruent with the *in vitro* data, and is consequent to the HT-induced inhibition of post-irradiation DNA damage repair which enhances the quadratic component of cell kill. These estimates should help to judiciously design and optimize RT dose-fractionation schedules for the clinical practice of HTRT and could

also assist in designing biologically effective thermoradiotherapy treatment planning systems.

Declaration of Competing Interest

There are no actual or potential conflicts of interest to declare.

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References

[1] van der Zee J, Vujaskovic Z, Kondo M, Sugahara T. The Kadota Fund International Forum 2004–clinical group consensus. Int J Hyperthermia 2008;24:111–22. https://doi.org/10.1080/02656730801895058.
[2] Dewhirst MW, Lee CT, Ashcraft KA. The future of biology in driving the field of hyperthermia. Int J Hyperthermia 2016;32:4–13. https://doi.org/10.3109/02656736.2015.1091093.
[3] Dewhirst MW, Vujaskovic Z, Jones E, Thrall D. Re-setting the biologic rationale for thermal therapy. Int J Hyperthermia 2005;21:779–90. https://doi.org/10.1080/02656730500271668.
[4] Overgaard J. The heat is (still) on–the past and future of hyperthermic radiation oncology. Radiother Oncol 2013;109:185–7. https://doi.org/10.1016/j.radonc.2013.11.004.
[5] Datta NR, Ordonez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and-/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev 2015;41:742–53. https://doi.org/10.1016/j.ctrv.2015.05.009.
[6] Dewhirst MW, Kirsch D. Technological advances, biologic rationales, and the associated success of chemotherapy with hyperthermia in improved outcomes in patients with sarcoma. JAMA Oncol 2018;4:493–4. https://doi.org/10.1001/jamaoncol.2017.4941.
[7] Repasky EA, Evans SS, Dewhirst MW. Temperature matters! And why it should matter to tumor immunologists. Cancer Immunol Res 2013;1:210–6. https://doi.org/10.1158/2326-6066.CIR-13-0118.
[8] Frey B, Weiss EM, Rubner Y, Wunderlich R, Ott OJ, Sauer R, et al. Old and new facts about hyperthermia-induced modulations of the immune system. Int J Hyperthermia 2012;28:528–42. https://doi.org/10.3109/02656736.2012.677933.
[9] Datta NR, Grobholz R, Puric E, Bode-Lesniewska B, Lomax N, Khan S, et al. Enhanced tumour regression in a patient of liposarcoma treated with radiotherapy and hyperthermia: hint for dynamic immunomodulation by hyperthermia. Int J Hyperthermia 2015;31:574–7. https://doi.org/10.3109/02656736.2015.1033482.
[10] Overgaard J, Gonzalez Gonzalez D, Hulshof MC, Arcangeli G, Dahl O, Mella O, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. Lancet 1995;345:540–3.
[11] Wessalowski R, Schneider DT, Mils O, Friemann V, Kyrillopoulou O, Schaper J, et al. Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: an open-label, non-randomised, single-institution, phase 2 study. Lancet Oncol 2013;14:843–52. https://doi.org/10.1016/s1470-2045(13)70271-7.
[12] van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000;355:1119–25.
[13] Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: The EORTC 62961-ESHO 95 randomized clinical trial. JAMA Oncol 2018;4:483–92. https://doi.org/10.1001/jamaoncol.2017.4996.
[14] Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys 2016;94:1073–87. https://doi.org/10.1016/j.ijrobp.2015.12.361.
[15] Datta NR, Rogers S, Klingbiel D, Gomez S, Puric E, Bodis S. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. Int J Hyperthermia 2016;32:809–21. https://doi.org/10.1080/02656736.2016.1195924.
[16] Datta NR, Rogers S, Ordonez SG, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: a systematic review and meta-analysis. Int J Hyperthermia 2016;32:31–40. https://doi.org/10.3109/02656736.2015.1099746.
[17] Datta NR, Stutz E, Gomez S, Bodis S. Efficacy and safety evaluation of the various therapeutic options in locally advanced cervix cancer: a systematic review and network meta-analysis of randomized clinical trials. Int J Radiat Oncol Biol Phys 2019;103:411–37. https://doi.org/10.1016/j.ijrobp.2018.09.037.
[18] Oei AL, Vriend LE, Crezee J, Franken NA, Krawczyk PM. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiat Oncol 2015;10:165. https://doi.org/10.1186/s13014-015-0462-0.
[19] Elming PB, Sorensen BS, Oei AL, Franken NAP, Crezee J, Overgaard J, et al. Hyperthermia: the optimal treatment to overcome radiation resistant hypoxia. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11010060.
[20] McMahon SJ. The linear quadratic model: usage, interpretation and challenges. Phys Med Biol 2018;64:01TR. https://doi.org/10.1088/1361-6560/aaf26a.
[21] Ihara M, Takeshita S, Okaichi K, Okumura Y, Ohnishi T. Heat exposure enhances radiosensitivity by depressing DNA-PK kinase activity during double strand break repair. Int J Hyperthermia 2014;30:102–9. https://doi.org/10.3109/02656736.2014.887793.
[22] Datta NR, Puric E, Schneider R, Weber DC, Rogers S, Bodis S. Could hyperthermia with proton therapy mimic carbon ion therapy? Exploring a thermo-radiobiological rationale. Int J Hyperthermia 2014;30:524–30. https://doi.org/10.3109/02656736.2014.963703.
[23] Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys 1982;8:1981–97.
[24] van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol 2018;13:96. https://doi.org/10.1186/s13014-018-1040-z.
[25] Guerrero M, Li XA. Analysis of a large number of clinical studies for breast cancer radiotherapy: estimation of radiobiological parameters for treatment planning. Phys Med Biol 2003;48:3307–26.
[26] Fowler JF. Sensitivity analysis of parameters in linear-quadratic radiobiologic modeling. Int J Radiat Oncol Biol Phys 2009;73:1532–7. https://doi.org/10.1016/j.ijrobp.2008.11.039.
[27] Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Semin Radiat Oncol 2008;18:234–9. https://doi.org/10.1016/j.semradonc.2008.04.004.
[28] Chapman JD. Can the two mechanisms of tumor cell killing by radiation be exploited for therapeutic gain? J Radiat Res 2014;55:2–9. https://doi.org/10.1093/jrr/rrt111.
[29] Fowler JF. 21 years of biologically effective dose. Br J Radiol 2010;83:554–68. https://doi.org/10.1259/bjr/31372149.
[30] Fowler JF. Optimum overall times II: extended modelling for head and neck radiotherapy. Clin Oncol (R Coll Radiol) 2008;20:113–26. https://doi.org/10.1016/j.clon.2007.11.003.
[31] Held KD, Kawamura H, Kaminuma T, Paz AE, Yoshida Y, Liu Q, et al. Effects of charged particles on human tumor cells. Front Oncol 2016;6:23. https://doi.org/10.3389/fonc.2016.00023.
[32] Bergs JW, Oei AL, Ten Cate R, Rodermond HM, Stalpers LJ, Barendsen GW, et al. Dynamics of chromosomal aberrations, induction of apoptosis, BRCA2 degradation and sensitization to radiation by hyperthermia. Int J Mol Med 2016;38:243–50. https://doi.org/10.3892/ijmm.2016.2611.
[33] Franken NA, Oei AL, Kok HP, Rodermond HM, Sminia P, Crezee J, et al. Cell survival and radiosensitisation: modulation of the linear and quadratic parameters of the LQ model (Review). Int J Oncol 2013;42:1501–15. https://doi.org/10.3892/ijo.2013.1857.
[34] Krawczyk PM, Eppink B, Essers J, Stap J, Rodermond H, Odijk H, et al. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. Proc Natl Acad Sci U S A 2011;108:9851–6. https://doi.org/10.1073/pnas.1101053108.
[35] Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, et al. Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer. Int J Radiat Oncol Biol Phys 2008;70:477–84. https://doi.org/10.1016/j.ijrobp.2007.06.035.
[36] Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996;35:731–44.
[37] Wen QL, He LJ, Ren PR, Chen CQ, Wu JB. Comparing radiotherapy with or without intracavitary hyperthermia in the treatment of primary nasopharyngeal carcinoma: a retrospective analysis. Tumori 2014;100:49–54. https://doi.org/10.1700/1430.15815.
[38] Huilgol NG, Gupta S, Sridhar CR. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: a report of randomized trial. J Cancer Res Ther 2010;6:492–6. https://doi.org/10.4103/0973-1482.77101.
[39] Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys 1994;28:163–9.

[40] Datta NR, Bose AK, Kapoor HK, Gupta S. Head and neck cancers: results of thermoradiotherapy versus radiotherapy. Int J Hyperthermia 1990;6:479–86.
[41] Arcangeli G, Benassi M, Cividalli A, Lovisolo GA, Mauro F. Radiotherapy and hyperthermia. Analysis of clinical results and identification of prognostic variables. Cancer 1987;60:950–6.
[42] Harima Y, Nagata K, Harima K, Ostapenko VV, Tanaka Y, Sawada S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int J Hyperthermia 2001;2009(25):338–43. https://doi.org/10.1080/02656730903092018.
[43] Franckena M, Stalpers LJ, Koper PC, Wiggenraad RG, Hoogenraad WJ, van Dijk JD, et al. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch Deep Hyperthermia Trial. Int J Radiat Oncol Biol Phys 2008;70:1176–82. https://doi.org/10.1016/j.ijrobp.2007.07.2348.
[44] Chen HW, Jei J, Wei L. A randomized trial of hyperthermoradiochemotherapy for uterine cervix. Chin J Oncol 1997;24:249–51.
[45] Datta NR, Bose AK, Kapoor HK. Thermoradiotherapy in the management of carcinoma cervix (stage IIIB): a controlled clinical study. Ind Med Gazette 1987;121:68–71.
[46] Comprehensive Meta-analysis Software, version 3.0 Available from Available from: http://www.meta-analysis.com/index.php Accessed on Accessed 25.10.2016.
[47] Higgins JPT, Green S. Cochrane handbook for systematic reviews and interventions. West Sussex, England: John Wiley & Sons Ltd.; 2008.
[48] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[49] Datta NR, Eberle B, Puric E, Meister A, Marder D, Tim O, et al. Is hyperthermia combined with radiotherapy adequate in elderly patients with muscle-invasive bladder cancers? Thermo-radiobiological implications from an audit of initial results. Int J Hyperthermia 2016;32:390–7. https://doi.org/10.3109/02656736.2015.1132340.
[50] van der Zee J, Gonzalez GD. The Dutch Deep Hyperthermia Trial: results in cervical cancer. Int J Hyperthermia 2002;18:1–12.
[51] Forster JC, Harriss-Phillips WM, Douglass MJ, Bezak E. A review of the development of tumor vasculature and its effects on the tumor microenvironment. Hypoxia (Auckl) 2017;5:21–32. https://doi.org/10.2147/HP.S133231.
[52] van Leeuwen CM, Oei AL, Chin K, Crezee J, Bel A, Westermann AM, et al. A short time interval between radiotherapy and hyperthermia reduces in-field recurrence and mortality in women with advanced cervical cancer. Radiat Oncol 2017;12:75. https://doi.org/10.1186/s13014-017-0813-0.
[53] Kroesen M, Mulder HT, van Holthe JML, Aangeenbrug AA, Mens JWM, van Doorn HC, et al. The effect of the time interval between radiation and hyperthermia on clinical outcome in 400 locally advanced cervical carcinoma patients. Front Oncol 2019;9:134. https://doi.org/10.3389/fonc.2019.00134.
[54] Borras JM, Grau C, Corral J, Wong K, Barton MB, Ferlay J, et al. Estimating the number of fractions by tumour site for European countries in 2012 and 2025: An ESTRO-HERO analysis. Radiother Oncol 2018;126:198–204. https://doi.org/10.1016/j.radonc.2017.11.009.
[55] Crezee H, van Leeuwen CM, Oei AL, Stalpers LJ, Bel A, Franken NA, et al. Thermoradiotherapy planning: integration in routine clinical practice. Int J Hyperthermia 2016;32:41–9. https://doi.org/10.3109/02656736.2015.1110757.
[56] van Leeuwen CM, Crezee J, Oei AL, Franken NAP, Stalpers LJA, Bel A, et al. The effect of time interval between radiotherapy and hyperthermia on planned equivalent radiation dose. Int J Hyperthermia 2018;34:901–9. https://doi.org/10.1080/02656736.2018.1468930.