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RESEARCH ARTICLE

Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis

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Abstract

Purpose: A systematic review and meta-analysis was conducted to evaluate the outcome of controlled clinical trials in head and neck cancers (HNCs) using hyperthermia and radiotherapy versus radiotherapy alone. *Material and methods*: A total of 498 abstracts were screened from four databases and hand searched as per the PRISMA guidelines. Only two-arm studies treating HNCs with either radiotherapy alone, or hyperthermia and radiotherapy without concurrent chemotherapy or surgery were considered. The evaluated end point was complete response (CR). *Results*: Following a detailed screening of the titles, abstracts and full text papers, six articles fulfilling the above eligibility criteria were considered. In total 451 clinical cases from six studies were included in the meta-analysis. Five of six trials were randomised. The overall CR with radiotherapy alone was 39.6% (92/232) and varied between 31.3% and 46.9% across the six trials. With thermoradiotherapy, the overall CR reported was 62.5% (137/219), (range 33.9–83.3%). The odds ratio was 2.92 (95% CI: 1.58–5.42, $p = 0.001$); the risk ratio was 1.61 (95% CI: 1.32–1.97, $p < 0.0001$) and the risk difference was 0.25 (95% CI: 0.12–0.39, $p < 0.0001$), all in favour of combined treatment with hyperthermia and radiotherapy over radiotherapy alone. Acute and late grade III/IV toxicities were reported to be similar in both the groups. *Conclusions*: Hyperthermia along with radiotherapy enhances the likelihood of CR in HNCs by around 25% compared to radiotherapy alone with no significant additional acute and late morbidities. This level I evidence should justify the integration of hyperthermia into the multimodality therapy of HNCs.

Introduction

The management of head and neck cancers (HNCs) involves a judicious combination of radiotherapy (RT), surgery and chemotherapy (CT). In a bid to improve therapeutic outcome, RT has been used either as a definitive treatment with altered fractionation regimes, or in combination with concurrent CT or the epidermal growth factor receptor inhibitor cetuximab [1–4]. As tumour hypoxia is known to confer radio resistance in HNCs, numerous clinical trials have been undertaken to explore sensitisation of the hypoxic cell fraction using normobaric oxygen and carbogen, hyperbaric oxygen or a wide range of pharmaceutical hypoxic cell sensitisers [5]. A systematic review of 4805 patients from 32 randomised trials provided level IA evidence that hypoxic cell sensitisation along with RT can achieve significantly improved rates of loco-regional tumour control, disease-specific survival, and overall survival in HNCs [5].

Hyperthermia (HT) at 39–45 °C, is considered to be one of the most potent radiosensitisers through inhibition of DNA damage repair, sensitisation of 'S' phase cells and hypoxic cell sensitisation, particularly of nutritionally deficient cells at low pH [6–8]. Thermoradiobiologically, HT complements the modes of action of low-LET radiation (X- and gamma rays) which show limited cytotoxicity in hypoxic cells, radio-resistant 'S' phase cells and also on the repair of sublethal/potentially lethal radiation-induced DNA damage. This complementary action of HT with RT is reflected in the favourable outcomes from clinical trials across a wide range of malignancies [7].

Another strong rationale for combining HT with RT is that it causes reoxygenation. These effects are long-lasting, affecting other RT treatment fractions, aside from the one given on the day of HT. Heat-induced reoxygenation has been demonstrated preclinically [9] and clinically in patients with locally advanced breast cancer [10], soft tissue sarcoma [11], and in companion canine soft tissue sarcomas [12,13]. In all cases, improvement in oxygenation after HT was associated with better response to thermoradiotherapy (HTRT). Furthermore, HT demonstrates additive or synergistic effects with a number of chemotherapeutic agents and both

thermochemotherapy (HTCT) and thermochemoradiotherapy (HTCTRT) have yielded encouraging results [7].

Most authors report a better outcome with combined HT and RT in HNCs when compared to historical controls or prospective case control studies [14–26]. Some studies were undertaken for specific disease sites, such as the nasopharynx or metastatic neck nodes, while others have included all head and neck tumour subsites. A few studies have reported their results along with other tumour sites (mixed tumour group) and the outcomes for HNCs were reported separately. However, these individual studies had a limited number of patients in the RT or HTRT treatment groups. These small sample sizes could result in some uncertainty in the interpretation of the study outcomes. Thus, a systematic review of the literature was undertaken and a meta-analysis performed to evaluate the efficacy of HTRT in terms of achieving complete response (CR) of the HNCs.

Materials and methods

Search strategy

The systematic review and meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines designed to improve the reporting of systematic reviews and meta-analysis [27]. The 27-item checklist and four-phase flow chart deal with identification of the records searched, screening of the records searched, assessing the eligibility of the short-listed articles after going through the full text and finally including studies that are considered for both qualitative and quantitative synthesis (meta-analysis).

For the present systematic review and meta-analysis, four databases, namely PubMed, Embase, Scopus and the Cochrane library were considered and they were last searched on 14 June 2015 (Figure 1). The MeSH terms used were 'Head and Neck Neoplasms' AND 'Radiotherapy' AND 'Hyperthermia, Induced'. The search was not limited to any date or language. Additional papers were retrieved through a hand search.

Inclusion criteria

Only two-arm studies (both randomised and non-randomised) fulfilling the following criteria were included: (1) HNCs treated with local HT and RT (those using concurrent CT, interstitial brachytherapy and/or surgery were excluded), (2) treatment outcome in terms of CRs were reported and (3) full text articles in English were available.
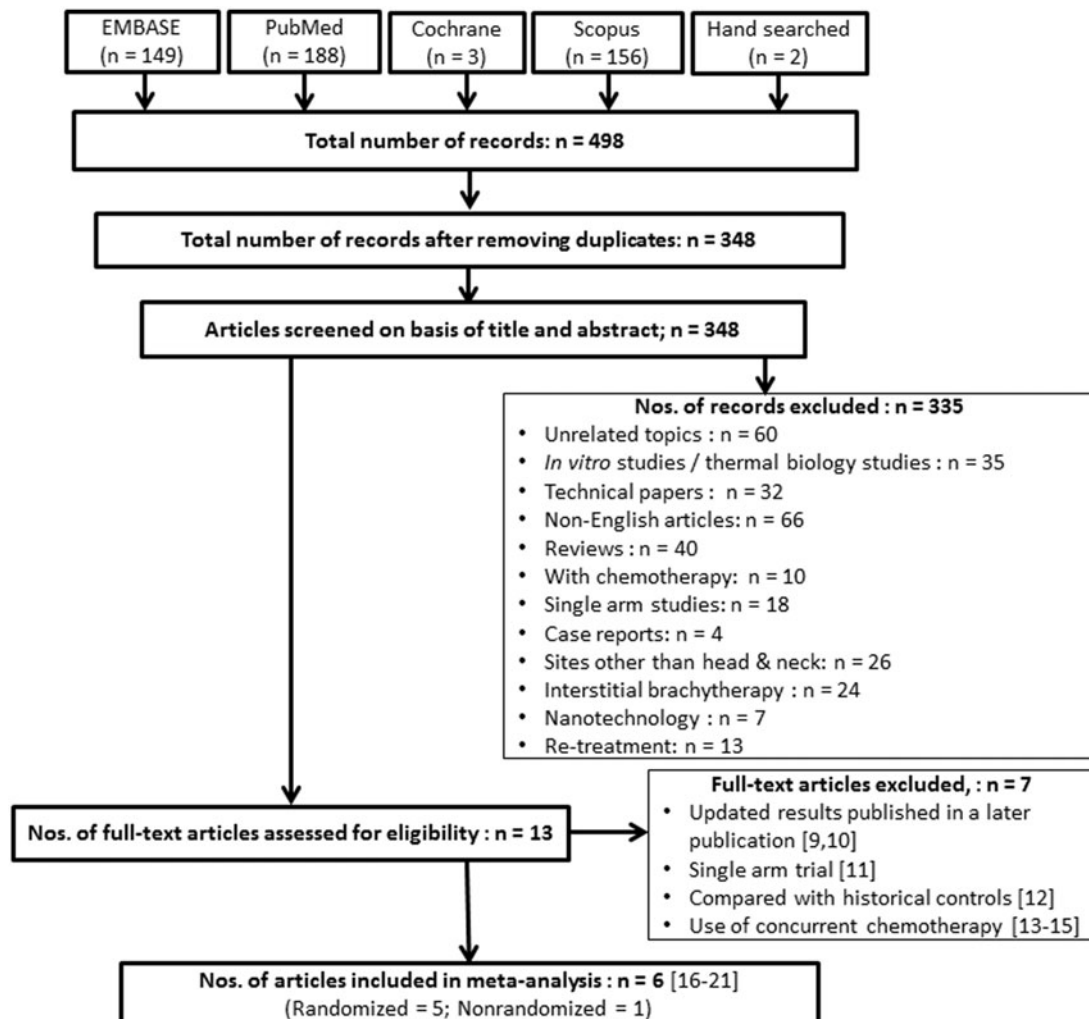

Figure 1. Flow-chart indicating the study selection procedure.

Study selection

Following exclusion of duplicates, articles were screened based on their titles and abstracts. Topics unrelated to HNCs, *in vitro* thermoradiobiological studies, technical papers on HT instrumentation, thermal dose, reviews, case reports, use of concurrent CT with RT and/or HT, use of interstitial brachytherapy, nanotechnology, re-treatments and non-English articles were excluded as detailed in Figure 1. Articles that had been updated in a later publication by the same author/s and those with mixed patient groups in which the outcomes for HNCs were not given separately were omitted.

Data extraction and quality assessment

The primary end point was CR at the end of treatment and was assessed by clinical examination or imaging studies. Details of the pre-treatment patient characteristics and RT and HT parameters were tabulated as per the information cited in the articles (Table 1). Although most of the studies reported CR in terms of number of patients (4/6), two studies expressed CR with respect to the number of lesions.

Acute and late toxicities were checked in each of the studies. As these studies were reported over a period of 27 years (1987–2014), uniform toxicity scoring criteria could not be expected. The toxicity and scoring criteria when available are given in Table 1.

Critical appraisal

Based on the pre-defined study criteria, study quality was assessed according to the PRISMA guidelines [27]. All possible factors relating to patient characteristics and treatment parameters that could have an impact on the outcome were evaluated. Only the studies that reported a CR for the patients treated with RT and HT, or where a CR could be calculated from the data presented in the articles were considered.

Statistical methods

The Comprehensive Meta-analysis Software package (version 3.0) was used to execute the meta-analysis [28]. The descriptive statistical analysis was carried out using IBM SPSS version 21.0 [29]. The odds ratio (OR), risk ratio (RR) and risk difference (RD) and numbers needed to treat (NNT) were calculated and the values expressed using a 95% confidence interval (CI) and the corresponding p values. Heterogeneity was assessed by the I^2 statistic, which represents the estimated proportion of unexplained inter-study variance prior to pooling of the studies. A random effect model was used for all analyses. The potential publication bias was evaluated by funnel plots and rank correlation tests with Kendall's tau [30]. All p values are two-sided and considered statistically significant if less than 0.05.

Results

A total of 498 articles were identified through the search and were screened as detailed in Figure 1. Following the exclusion of duplicates, 348 articles were screened based on their title and abstracts and 335 of these were omitted as they did not meet the inclusion criteria. Thirteen articles were shortlisted for full text review from which seven articles were further excluded as detailed in Figure 1 [14–20]. Six articles involving 451 clinical cases, of which 232 were treated with RT alone and 219 by HTRT, were subjected to the meta-analysis (Table 1) [21–26].

Five of these six studies were randomised trials. One study was carried out exclusively in nasopharyngeal tumours [21], while others were for all HNCs. Most of the patients included had locally advanced stage III or IV tumours. No concurrent CT or surgery was used. The RT dose varied from 32–80 Gy and was usually delivered at 1.8–2 Gy per fraction. Perez et al. [24] delivered 32 Gy at 4 Gy per fraction twice a week, while Arcangeli et al. [26] treated their patients with three fractions per day of 1.5–2 Gy each with an interfraction interval of 4 h.

Hyperthermia was delivered using microwaves ($n = 2$) or radiofrequency ($n = 4$) at 8–915 Mhz and the time intervals varied from immediate to 60 min (Table 1). In all but one study HT was applied after RT [25]. Four trials used HT twice a week along with RT, while it was used once a week by Huilgol et al. [22] and on alternate days by Arcangeli et al. [26]. In most studies, a temperature of 42.5 °C was attained and maintained for 20–45 min. Single or multi-sensor invasive thermometry using thermistors or thermocouples was used in these studies. Wen et al. [21] used thermometry probes attached to their applicator for tumour surface temperature measurements. The details of the HT and RT parameters for each study are stated in Table 1.

With RT alone, an overall CR of 39.6% (92/232) was reported and this varied between 31.3% and 46.9% across the six trials. The overall CR with HTRT was 62.5% (137/219), and ranged from 33.9% to 83.3%. The resultant OR was 2.92 (95% CI: 1.58–5.42, $p = 0.001$) with I^2 of 55.38 ($p = 0.047$) (Figure 2a). The corresponding RR was 1.61 (95% CI: 1.32–1.97, $p < 0.0001$, $I^2 = 13.37$, $p = 0.329$) and RD was 0.25 (95% CI: 0.12–0.39, $p < 0.0001$, $I^2 = 59.44$, $p = 0.031$) in favour of combined treatment with HT and RT over RT alone (Figure 2b and c). The funnel plots and the Kendall's tau for OR, RR and RD did not show any publication bias (Figure 3). However, this should be interpreted with caution considering the limited number of studies available for this meta-analysis [30].

The toxicity observed in these patients for each study is indicated in Table 1. It was not feasible to compute the toxicity profiles as the acute and late toxicities were not uniformly reported based on standard scoring criteria. However, none of the studies reported any significant increase in toxicities with HTRT compared to RT alone.

Discussion

Radiation therapy in HNCs is known to offer an advantage in terms of organ preservation and function. This has been feasible in early T1 and T2 tumours with an acceptable local control of 70–90%. However, RT alone is often inadequate for T3–T4 tumours and concurrent CT, biological therapies or altered fractionation strategies are required to improve treatment outcomes. These could be associated with increased toxicity depending on the treatment intensification [1–3,31]. The adoption of newer treatment techniques, such as intensity-modulated radiotherapy (IMRT) supported by image

Table 1. Summary of the key patient and treatment characteristics along with the outcome of the head and neck studies (radiotherapy versus radiotherapy and hyperthermia) included in the meta-analysis.

Author, year	Site	TNM stage	RT dose (Gy)	Type of HT	HT and RT sequence and time interval	Mean HT temperature (°C) and thermometry	HT duration (min)	HT sessions/week	Total no. of HT sessions*	RT group No. CR/Total	RT group % CR	RT+HT group No. CR/Total	RT+HT group % CR	Remarks
Wen et al., 2014 [21]	NP	II–IVa	60–80 (2 Gy/fr) with cobalt or linac, technique not stated	MW	Post-RT 10–60 min	44–52 °C at tumour surface, 98% of tumour surface at 44.4 °C	60	2	Mean: 6	23/49	46.9	34/49	69.4	Randomised; intracavitary HT; CR based on imaging studies; LPFS and PFS significantly better with HTRT (median PFS: 100 vs. 60 months, median LPFS 111 vs. 54 months for HTRT vs. RT respectively); toxicity assessed as per RTOG and NCI CTC criteria and similar for both groups
Huilgol et al., 2010 [22]	OC OP HP	II–IV	Mean: 66.9–67.5 (2 Gy/fr) parallel opposed portals	RF	Post-RT Time interval not stated	Tav 42.3 °C single point invasive thermometry	30	1	5–7	11/26	42.3	22/28	78.6	Randomised; median survival better in HTRT group (241 days vs. 145 days for HTRT and RT respectively); toxicity assessment criteria not stated; toxicities comparable in both groups, no dose-limiting thermal burns or excessive mucosal or thermal toxicity reported
Valdagni et al., 1994 [23]	NN (N3)	IV	64–70 (2–2.5 Gy/fr) single/ parallel opposed portals	RF	Post-RT 20–25 min	T_{min} 42.5 °C multi-point invasive thermometry	Lowest temp of 42.5 °C maintained for 30 min	2	12	9/22	40.9	15/18	83.3	Randomised; 5-year LC: 24.2% vs. 68.6% with RT and HTRT respectively ($p = 0.015$); 5-year OS 53.3% vs. 0% with RT and HTRT respectively ($p = 0.02$); RTOG/EORTC criteria, acute toxicity similar in both arms except 1 patient had burns in HTRT group, 2 patients developed bone necrosis with HTRT attributed to nodes fixed to mandible
Perez et al., 1991 [24]	HN	NA	32 (4 Gy/fr × 8) twice weekly single/ parallel opposed portals	MW	Post-RT 15–30 min	42.5 °C multipoint thermometry	60	2	8	21/60	35.0	18/53	33.9	Randomised; only HNC patients considered; outcomes reported as lesions; 30% received <90% of 32 Gy prescribed RT dose; only 52% of HTRT group received prescribed RT dose and 8 sessions of HT; toxicity score based on RTOG criteria; except for 30% incidence of thermal blisters acute and late toxicities comparable in both groups; separate survival outcomes for HNCs not stated

Author, year	Site	TNM stage	RT dose (Gy)	Type of HT	HT and RT sequence and time interval	Mean HT temperature (°C) and thermometry	HT duration (min)	HT sessions/ week	Total no. of HT sessions*	RT group No. CR/ Total	RT group % CR	RT + HT group No. CR/ Total	RT + HT group % CR	Remarks
Datta et al., 1990 [25]	OC OP	I–IV	60–65 (2 Gy/fr) parallel opposed portals	RF	Pre-RT immediate	42.5 °C single point invasive thermometry	20 min after attaining required temp	2	12	10/32	31.3	18/33	54.5	Randomised; response was better with HTRT in stages III/IV; DFS at 18 months 19% with RT vs. 33% with HTRT; toxicity assessment criteria not stated; toxicity comparable in both arms
Arcangeli et al., 1987 [26]	NN	NA	60 (3 fr/day 1.5–2 Gy each) single/ parallel opposed portals	RF MW	Post-RT immediate	42.5 °C single or multipoint thermometry	45	3	7	18/43	41.9	30/38	78.9	Non-randomised; only head neck patients considered; CR rates given as number of lesions; LC at 2 years 58% vs. 14% with HTRT and RT respectively; toxicity assessment criteria not stated; no significant increase in toxicity seen with HT

HT, hyperthermia; RT, radiotherapy; HTRT, thermoradiotherapy; NA, not available; HNCs, head and neck cancers; NP, nasopharynx; OC, oral cavity; OP, oropharynx; HP, hypopharynx; NN, neck node; HN, head neck, no specific site stated; MW, microwave; RF, radiofrequency; RRT, radical radiotherapy; PRT, preoperative radiotherapy; CR, complete response; PFS, progression-free survival; LPFS, Local progression-free survival; DFS, disease-free survival; LC, local control; OS, overall survival.

guidance, has shown that treatment-related morbidities for patients with HNCs can be reduced, resulting in an improved quality of life [32].

Several groups reporting both single-arm and controlled clinical trials have advocated HT with RT, CT or both over the past four decades. This was based on the strong thermo-radiobiological basis of HT and its sensitising abilities to RT and CT [5–9,12]. However, with the technological advancements in HT treatment delivery, treatment planning and thermometry, HT can now be delivered with more certainty, thereby ensuring safer and more effective treatment without significant additional morbidity [7].

Although some of the individual studies carried out in locally advanced HNCs have been promising, HT has still failed to gain popularity among the oncology community. This is perhaps due to a lack of adequate-sized randomised clinical trials, a dearth of HT equipment tailored to the head neck region, inadequate thermometry, and paucity of HT treatment planning software. The present systematic review and meta-analysis was undertaken to evaluate the outcomes of all previous trials using HTRT versus RT alone to seek a level I evidence of the effectiveness of HTRT in HNCs.

Several studies have shown that CR is a strong predictor of survival in HNCs [33,34]. In addition, Michiels et al. [35] used individual patient data from 104 trials that included 22,744 irradiated patients to show that locoregional control and event-free survival correlated with overall survival in locally advanced HNCs. We therefore chose attainment of CR at the end of definitive treatment by RT or HTRT as the primary end point.

Five of the six trials reported the long-term survival outcomes using different end points (Table 1). It was evident that the HTRT patients fared better compared to RT alone in all studies. The longest survival figures reported by Valdagni et al. [23] show that patients with HTRT had significantly better freedom from local relapse (HTRT versus RT: 68.6% versus 24.2%, $p = 0.015$) and overall survival (HTRT versus RT: 53.3% versus 0%, $p = 0.02$) at 5 years. The Radiation Therapy Oncology Group (RTOG) trial reported by Perez et al. [24] did not report the survival outcomes separately for HNCs.

The OR, RR and RD in this meta-analysis all indicate that a significantly better outcome was achieved with HTRT as compared with RT alone. However, it was also noted that there was significant heterogeneity as indicated by the I^2 statistics for OR ($I^2 = 55.38$, $p = 0.047$) and RD ($I^2 = 59.44$, $p = 0.031$) (Figures 2a and c). The forest plots suggest that this could be due to the outcomes reported by Perez et al. where no significant advantage was evident with HTRT over RT alone [24].

To explore the cause of the heterogeneity, the computation of OR, RR and RD were repeated by excluding the RTOG trial reported by Perez et al. [24]. This resulted in a revised OR of 3.69 (95% CI: 2.32–5.89, $I^2 = 0.000$, $p = 0.618$), RR of 1.74 (95% CI: 1.43–2.13, $I^2 = 0.000$, $p = 0.847$) and RD of 0.31 (95% CI: 0.21–0.41, $I^2 = 0.000$, $p = 0.656$). The revised calculations show a significant fall in I^2 values to 0.000, indicating no heterogeneity in the outcomes from the remaining five trials. This confirmed that the heterogeneity was solely due to the results from Perez et al. [24]. However,

(a) Odds ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)

Study name	Odds ratio	Lower limit	Upper limit	p-Value	RT+HT	RT alone	Relative weight	
Wen et al, 2014	2.56	1.12	5.86	0.026	34 / 49	23 / 49	19.89	
Huilgol et al, 2010	5.00	1.52	16.46	0.008	22 / 28	11 / 26	14.36	
Valdagni et al, 1994	7.22	1.61	32.46	0.010	15 / 18	9 / 22	10.90	
Perez et al, 1991	0.96	0.44	2.08	0.908	18 / 53	21 / 60	20.75	
Datta et al, 1990	2.64	0.96	7.28	0.061	18 / 33	10 / 32	16.85	
Arcangeli et al, 1987	5.21	1.94	13.98	0.001	30 / 38	18 / 43	17.26	
Overall effect	2.92	1.58	5.42	0.001	137 / 219	92 / 232		

Test for heterogeneity, $I^2 = 55.38$, $p = 0.047$

Favours RT Favours RT+HT

(b) Risk ratio (Radiotherapy + Hyperthermia vs. Radiotherapy alone)

Study name	Risk ratio	Lower limit	Upper limit	p-Value	RT+HT	RT alone	Relative weight	
Wen et al, 2014	1.48	1.04	2.10	0.029	34 / 49	23 / 49	26.11	
Huilgol et al, 2010	1.86	1.14	3.03	0.013	22 / 28	11 / 26	15.00	
Valdagni et al, 1994	2.04	1.18	3.51	0.010	15 / 18	9 / 22	12.44	
Perez et al, 1991	0.97	0.58	1.62	0.908	18 / 53	21 / 60	13.93	
Datta et al, 1990	1.75	0.96	3.18	0.069	18 / 33	10 / 32	10.35	
Arcangeli et al, 1987	1.89	1.28	2.78	0.001	30 / 38	18 / 43	22.16	
Overall effect	1.61	1.32	1.97	0.000	137 / 219	92 / 232		

Test for heterogeneity, $I^2 = 13.37$, $p = 0.329$

Favours RT Favours RT+HT

(C) Risk difference (Radiotherapy + Hyperthermia vs. Radiotherapy alone)

Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	p-Value	RT+HT	RT alone	Relative weight	Relative weight	
Wen et al, 2014	0.22	0.10	0.01	0.03	0.41	0.021	34 / 49	23 / 49	18.39		
Huilgol et al, 2010	0.36	0.12	0.02	0.12	0.61	0.003	22 / 28	11 / 26	15.02		
Valdagni et al, 1994	0.42	0.14	0.02	0.16	0.69	0.002	15 / 18	9 / 22	13.64		
Perez et al, 1991	-0.01	0.09	0.01	-0.19	0.17	0.908	18 / 53	21 / 60	19.40		
Datta et al, 1990	0.23	0.12	0.01	-0.00	0.47	0.051	18 / 33	10 / 32	15.58		
Arcangeli et al, 1987	0.37	0.10	0.01	0.17	0.57	0.000	30 / 38	18 / 43	17.97		
Overall effect	0.25	0.07	0.00	0.12	0.39	0.000	137 / 219	92 / 232			

Test for heterogeneity, $I^2 = 59.44$, $p = 0.031$
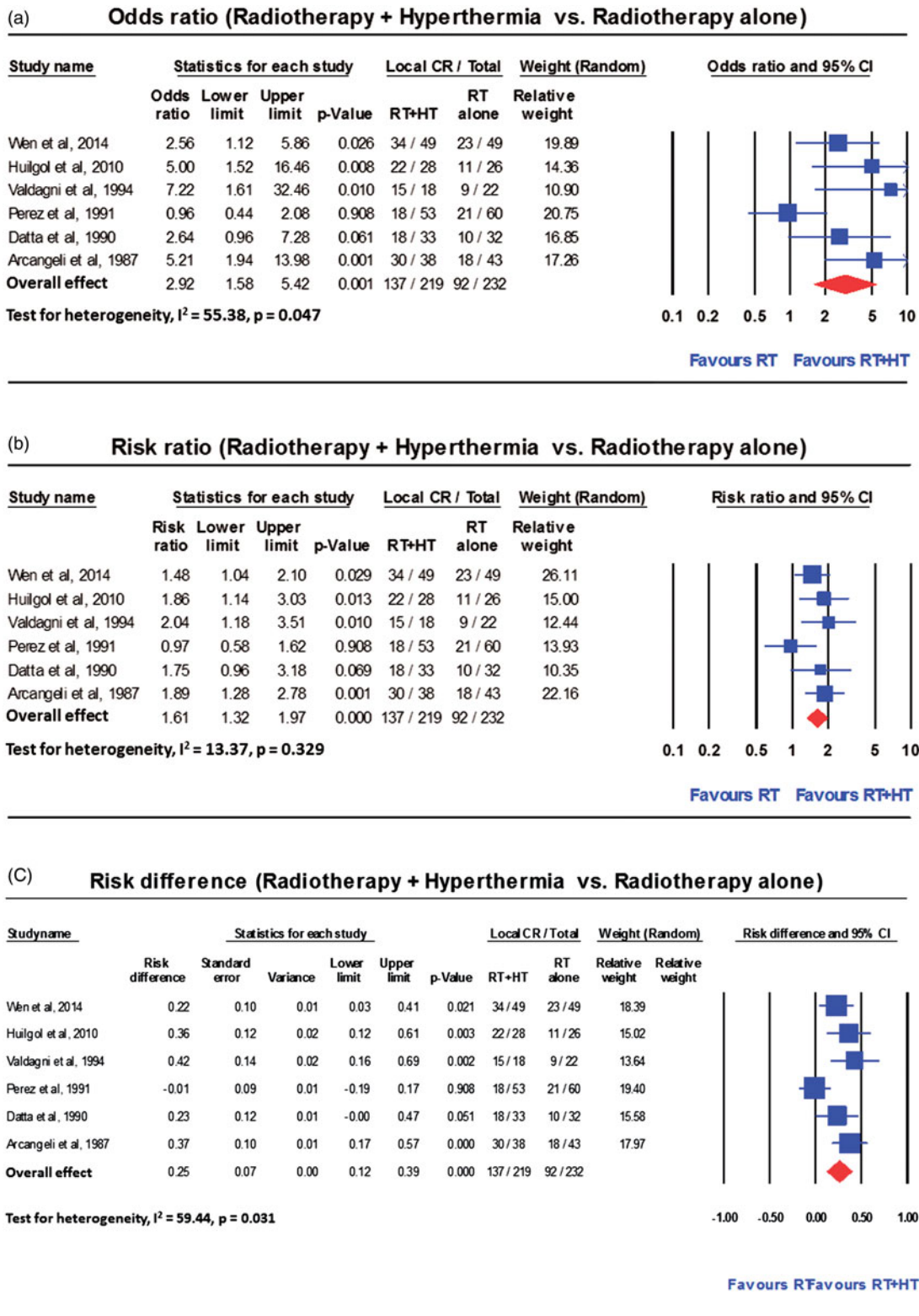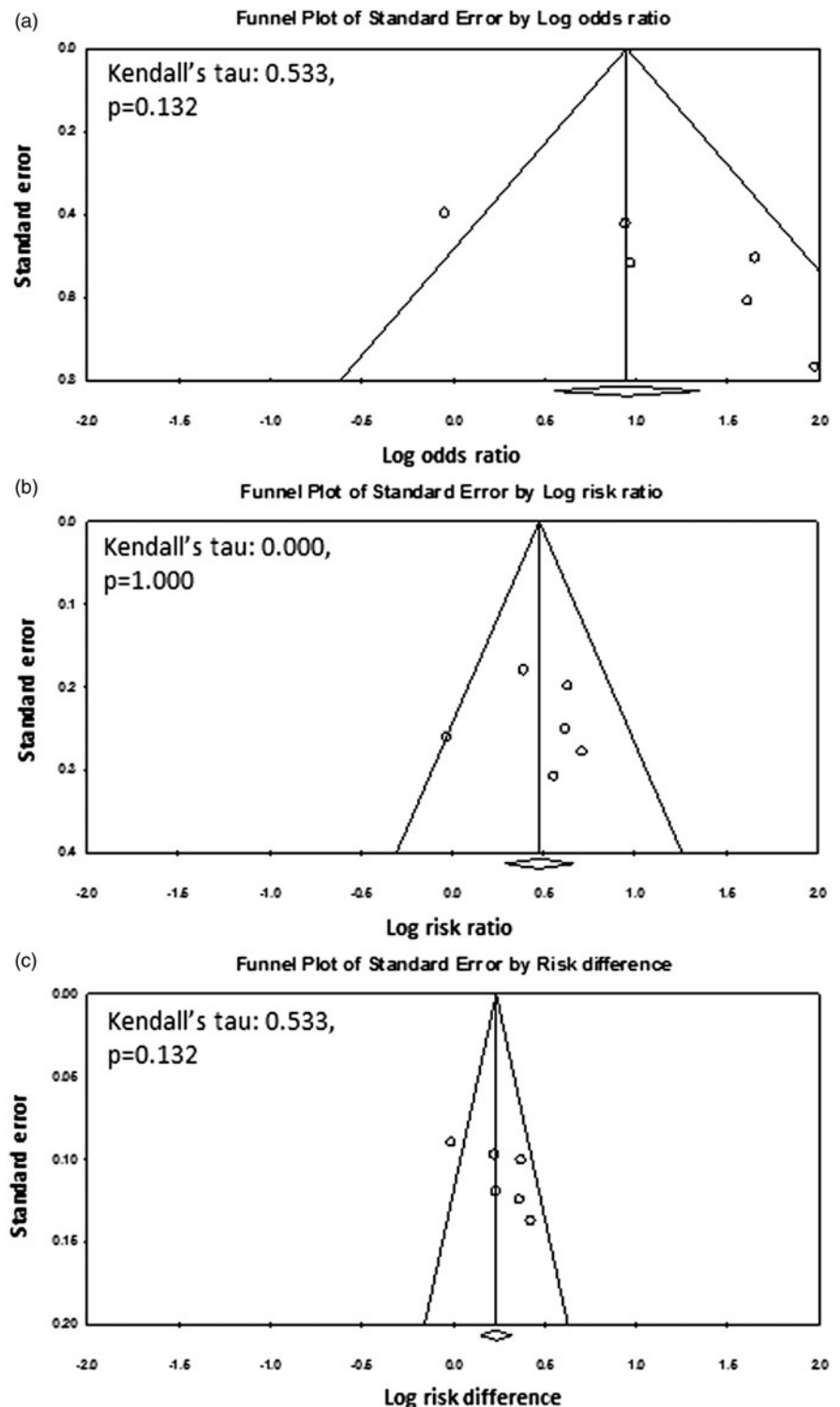
Favours RT Favours RT+HT

Figure 2. Forest plots from the six individual two-arm studies depicting (a) the odds ratio, (b) risk ratio, (c) risk difference.

the effect measures from the five studies remained similar to the original values. A closer perusal of the RTOG study from Perez et al. [24] revealed that the phase III trial was for a mixed patient group of 307 patients, in whom 113 lesions pertained to HNCs. The authors stated that 50% of all the lesions in the trial had been previously treated with irradiation. No separate outcomes were available for those being re-irradiated. Moreover, 30% of the patients received less than 90% of the prescribed RT dose (32 Gy). Only 52% of the patients of the HTRT arm were treated as per the desired RT and HT dose schedules outlined in the protocol. Furthermore, only 56% of the lesions less than 3 cm in diameter and 36% of larger tumours received 'adequate' therapy. Thus, a negative outcome in patients subjected to HTRT in this study should be considered in the context of these mitigating factors. This paper highlights the need for proper patient selection,

Figure 3. Funnel plots along with the Kendall's tau and the *p* values for (a) odds ratio, (b) risk ratio and (c) risk difference for clinical trials with radiotherapy alone versus radiotherapy and hyperthermia.

(a) Funnel Plot of Standard Error by Log odds ratio

Kendall's tau: 0.533, p=0.132

(b) Funnel Plot of Standard Error by Log risk ratio

Kendall's tau: 0.000, p=1.000

(c) Funnel Plot of Standard Error by Risk difference

Kendall's tau: 0.533, p=0.132

adequate heating techniques and patient compliance before a therapeutic intervention is judged not to be beneficial. Furthermore, on evaluating the reasons for the negative results, it became evident that there were also issues due to the lack of quality assurance in the delivery of HT [36]. This eventually led to the establishment of RTOG guidelines for conduct of HTRT trials [37].

Evidence from this meta-analysis indicates that HTRT can improve therapeutic outcomes compared to RT alone. The significant RD of 0.25 (increase in CR of at least 25%) could translate into better survival outcomes with HTRT.

Particularly promising is that HT, unlike modalities such as CT or biotherapies, may not add to the morbidity of RT. As concurrent chemoradiotherapy (CTRT) is one of the accepted treatment approaches in locally advanced HNCs, it would also be worth exploring the integration of HT with CTRT, especially with cisplatin.

Cisplatin is an active component of most CTRT regimes in HNCs [1]. Further, preclinical studies and various phase I/II clinical have shown that trimodality therapy with cisplatin and HTRT can achieve a synergistic effect which could translate into clinical efficacy [38]. Two recent randomised trials in

nasopharyngeal cancer compared HTRT versus RT alone. Cisplatin was used in both arms [18,19]. Kang et al. [18] randomised 154 patients with stages N2 and N3 nasopharyngeal carcinoma to receive either CTRT ($n = 78$) or HTCTRT. They observed a significantly better CR and 5-year overall survival in patients treated with HTCTRT compared to CTRT alone (CR: 81.6% versus 62.8%, $p < 0.05$, 5-year overall survival 68.4% versus 50%, $p < 0.05$ for HTCTRT and CTRT respectively). Hua et al. [19] randomised 180 patients with nasopharyngeal cancers (all stages) to either CTRT ($n = 90$) or HTCTRT ($n = 90$). Chemotherapy consisted of cisplatin and 5-FU. Patients with HTCTRT had a better CR rate (HTCTRT versus CTRT: 95.6% versus 81.1%, $p = 0.003$) and 5-year progression-free survival (HTCTRT versus CTRT: 72.7% versus 63.1%, $p = 0.039$). Acute and late morbidities were comparable in both groups. Thus, these studies showed that HTCTRT with cisplatin is safe, feasible and more effective than CTRT alone. Consequently, the addition of HT could be explored in other HNC subsites where cisplatin is an integral part of the CTRT treatment.

There has been considerable interest in the human papillomavirus (HPV) positive head and neck tumours and their enhanced sensitivity to radiation [39–41]. Similar observations are also evident for cervical cancers [42,43]. A number of mechanisms have been proposed to explain the relative radiosensitivity of these HPV tumours [44]. For example, HPV could cause a temporary down regulation of the p53 and pRb pathways. During the course of radiotherapy, a gradual reduction in HPV levels could result in the repression of E6 and E7 oncoproteins, resulting in restoration of the dormant p53 and pRb apoptotic pathways [45]. Recently, it has also been shown that exposure of HPV positive cell lines to a temperature of 42 °C for 1 h resulted in E6 degradation, thereby preventing the formation of the E6-p53 complex. p53-dependent apoptosis and G2-phase arrest ensued [46]. Thus, HT along with RT could result in a synergistic effect that would be particularly effective for the HPV positive HNCs. Moreover, HT has also been shown to be a strong immunomodulator, which could further enhance tumour response in HPV positive tumours [7,47].

HPV status was not reported in the six studies included in this meta-analysis and it was not possible to ascertain the effect of HTRT in HPV positive patients as it is increasingly becoming apparent that HPV-positive patients need less intensive treatment due to the increased radiosensitivity of these tumours [48]. Based on the emerging preclinical evidence of synergy, HTRT should be evaluated as a less toxic therapy in future trials of HPV positive head and neck cancers.

As evident from this meta-analysis, a risk difference of 0.25 in favour of HTRT over RT alone results in a NNT figure of 4 with HTRT (Figure 2c). This has been achieved with neither the RT nor HT being carried out with state-of-the-art techniques. Most patients in these trials were irradiated using parallel opposed portals along with single or multiple point-based thermometry. However, with the availability of IMRT and image guidance, RT dose intensification with effective sparing of the organs at risk may result in an improved therapeutic ratio. Similarly, the recent developments in HT techniques in HNCs include special hyperthermia head and

neck applicators [49], feasibility of HT treatment planning [50–53], non-invasive magnetic resonance-based thermometry [54] and the use of integrated online complaint-adaptive steering of specific absorption rate (SAR) during real time HT sessions [55]. All these could improve the delivery of HT and allay the initial scepticism regarding the efficacy and safety of HT.

With the strong clinical evidence that HTRT improves outcome without additional morbidity compared with RT alone in HNCs, HT should be integrated as a key therapeutic component in the multimodality therapy of these tumours in routine clinical practice. However, well-designed randomised trials are required to determine whether the therapeutic efficacy of HTRT could be further augmented using triple modality treatment in the management of locally advanced HNCs with acceptable morbidity. The trials could be designed to answer whether 1) HTRT is an effective treatment for HPV positive HNCs, and 2) HTRT can be considered an effective alternative to concurrent CTRT with a lower morbidity. This would require a three-arm phase III randomised trial in locally advanced HNCs with CTRT (as control arm) versus HTRT versus HTCTRT. HPV status could be incorporated as a stratification factor in the trial design and a subgroup analysis with an adequate sample size could be conducted to explore the outcomes according to HPV status. Such a trial would be paramount in defining the place of HT in the management of locally advanced HNCs.

Conclusion

The present systematic review and meta-analysis provides level I evidence of the efficacy of HTRT over RT alone in HNCs. With the current availability of sophisticated hardware and software for HT treatment delivery and monitoring, it is time to integrate HT as an essential component of the multimodality therapeutic approach, especially for locally advanced HNCs. Future randomised trials are needed to evaluate the addition of concurrent CT to HTRT and also to examine the role of HTRT in HPV positive tumours.

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Declaration of interest

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