Cancer Treatment Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future

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ARTICLE INFO

Article history:
Received 21 March 2015
Received in revised form 16 May 2015
Accepted 20 May 2015
Available online xxxx

Keywords:
Hyperthermia
Clinical trials
Radiotherapy
Chemotherapy
Thermal dose
Treatment planning

ABSTRACT

Hyperthermia, one of the oldest forms of cancer treatment involves selective heating of tumor tissues to temperatures ranging between 39 and 45 °C. Recent developments based on the thermoradiobiological rationale of hyperthermia indicate it to be a potent radio- and chemosensitizer. This has been further corroborated through positive clinical outcomes in various tumor sites using thermoradiotherapy or thermoradiochemotherapy approaches. Moreover, being devoid of any additional significant toxicity, hyperthermia has been safely used with low or moderate doses of reirradiation for retreatment of previously treated and recurrent tumors, resulting in significant tumor regression. Recent *in vitro* and *in vivo* studies also indicate a unique immunomodulating prospect of hyperthermia, especially when combined with radiotherapy. In addition, the technological advances over the last decade both in hardware and software have led to potent and even safer loco-regional hyperthermia treatment delivery, thermal treatment planning, thermal dose monitoring through noninvasive thermometry and online adaptive temperature modulation. The review summarizes the outcomes from various clinical studies (both randomized and nonrandomized) where hyperthermia is used as a thermal sensitizer of radiotherapy and-/or chemotherapy in various solid tumors and presents an overview of the progresses in loco-regional hyperthermia. These recent developments, supported by positive clinical outcomes should merit hyperthermia to be incorporated in the therapeutic armamentarium as a safe and an effective addendum to the existing oncological treatment modalities.

Introduction

Hyperthermia, one of the oldest forms of a cancer treatment known to mankind, was first mentioned in the Edwin Smith Surgical Papyrus around 5000 BC [1]. The Indian medical treatises of *Charak Samhita* and *Sushrut Samhita* scripted in about 3000 BC also mentions hyperthermia as a therapeutic modality [2]. Hippocrates too, had acknowledged the potential of "heat" for cancer treatment and had stated that tumors which cannot be cured by heat must be deemed incurable. Several reports of tumor regression following high fever secondary to bacterial infections, like erysipelas are available in the 19th century [3–5]. However, with the discovery of penicillin in 1930s, as high fever secondary to these infections became a rarity, the phenomenon of tumor regressions following high fever too became infrequently reported.

According to the Kadota Fund International Forum 2004, hyperthermia is usually defined as a modest elevation of temperature in the range of 39–45 °C [6]. Temperatures beyond this are considered as thermal ablation. The resurgence of hyperthermia for cancer therapy came subsequent to the several *in vitro* and *in vivo* studies carried out during the latter half of the last century following systematic evidence of a thermal dependence of cell kill and its potentiation by radiotherapy [7–9]. This prompted clinicians to use

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http://dx.doi.org/10.1016/j.ctrv.2015.05.009
0305-7372/

hyperthermia either alone or in combination with radiotherapy or chemotherapy for various tumor sites. Nonetheless, by the end of the last century, there was a subtle dampening in the enthusiasm for hyperthermia in clinical practice. This was due to a lack of proper heating and temperature monitoring equipment and some equivocal reports on treatment outcomes that could be attributed to unsatisfactory heating techniques [10–13].

Since the beginning of this century, there has been resurgence in hyperthermia with insights redefining the biological rationale of hyperthermia, immunomodulation at higher temperatures along with the availability of better hard and software permitting safer and more effective hyperthermia treatment delivery. The present review summarizes these developments that make hyperthermia a potent and viable complement to the existing treatment modalities in future oncology management.

Hyperthermia can be used both as a thermal sensitizer and thermal ablator. In this article, we intend to focus primarily on the developments related to hyperthermia as a thermal sensitizer adjuvant to radiotherapy and-/or chemotherapy in solid tumors. Thus, certain thermoablative techniques like high-intensity focused ultrasound and radiofrequency ablation are outside the scope of this review.

Mode of action of hyperthermia

Thermobiological rationale of hyperthermia

Various *in vitro* and *in vivo* studies conducted during 1970s to 2000s have conclusively shown that radiation induced damage is enhanced by hyperthermia at 41–43 °C. These have been very well summarized in various reviews [7–9]. Primarily, the thermal sensitizing effects with radiotherapy are due to (a) increased sensitivity of hypoxic, nutritionally deficient cells in low pH (b) inhibition of radiation induced DNA damage repair (c) sensitization of the "S" phase cells and (d) an enhanced intrinsic sensitivity of some tumor cells to hyperthermia (e.g. sarcomas, melanomas). All these contribute to a relative radioresistance with conventional photon therapy and hence addition of hyperthermia to radiation could yield a supplementary effect on tumor cytotoxicity.

Furthermore, hyperthermia with its properties as mentioned above, shares the radiobiological advantages as evident in high linear energy transfer (LET) radiations, like ^{12}C particle. Robinson therefore described hyperthermia as a "poor man's high-LET radiation" [14]. Thus, in combination with protons (physical dose profile similar to that of ^{12}C ions), hyperthermia (with its high-LET properties comparable to ^{12}C ions) could even mimic ^{12}C ion therapy [14].

Chemotherapeutic agents and hyperthermia appear to have a three-way interaction. Some drugs like 5-flurouracil, methotrexate, taxanes have an independent action and hence may not be potentiated with hyperthermia. An additive action on tumor cell kill with increasing temperature is evident with drugs like doxorubicin, cyclophosphamide, ifosphamide, gemcitabine, etc. A distinct sensitization and synergistic action at temperatures of 41–43 °C could be appreciated with cisplatin, carboplatin and bleomycin [15].

Even though these observations are based on *in vitro* studies for tumors heated at or beyond 43 °C, Dewhirst et al., have indicated that even in the temperature range of 39–42 °C, biological effects of hyperthermia could be evident through inhibition of radiation induced damage repair, changes in perfusions, re-oxygenation, induction of heat shock proteins (HSP) and immunomodulation [16]. This could reset the biological rationale for thermal therapy and may permit the use of hyperthermia even at lower temperatures that are easily achievable and better tolerated by the patients during hyperthermia treatment sessions.

Immune modulation induced by hyperthermia

In addition to the various thermoradiobiological effects that have been discussed above, it has been lately shown that local hyperthermia has also the capability of inducing systemic anti-tumor immune responses [17]. The latter had been described in the past only after whole-body hyperthermia. The mode of action is related to mechanisms induced by fever as a component of the acute phase immune response to injury or infection [18,19]. Innate immune responses are induced by binding of pathogen associated molecular patterns (PAMPs) to Toll-like receptors (TLRs), such as prototypic pattern recognition receptors. In cancer, whole body hyperthermia might additionally improve the adaptive immunity to tumor antigens by induction of dendritic cell (DC) maturation, activation, migration, increasing the tumor antigen presentation and stimulating the activation and trafficking of leukocytes, just to mention as some of the main modes of such immune interactions [20].

Local irradiation in association with mild hyperthermia has been demonstrated to result in systemic effects through immune mediated abscopal effects [21,22]. The local modification of the phenotype of the tumor cells and their microenvironment might render the tumor immunogenic. The key players in this scenario in the tumor microenvironment are the damage associated molecular patterns (DAMPs); danger signals such as high mobility group box 1 (HMGB1) protein, adenosine triphosphate (ATP) and HSP70. HMGB1 and HSP70 bind both to TLR4 and thus enhance the processing of tumor antigens by DCs and their cross-presentation to T cells [23,24]. HSP70, being a chaperone, has cyto-protective tasks inside the cell. It stimulates the immune system by activating DCs and NK cells when present in the extracellular space [25,26]. Since HSPs are much conserved and bear the ability to activate antigen presenting cells (APCs), they provide a unified mechanism for response to internal and external stimuli [27]. HSP70 chaperone peptides are a part of the stress response and thus can transfer tumor proteins to DCs, which could then cross-present these antigens and initiate an adaptive immune response [28].

Thus, tumor peptides bound to HSP70 are delivered to DCs that act as antigen-presenting cells and free HSP70 could stimulate the consecutive cross-presentation of tumor antigens to cytotoxic CD8+ T cells. The latter specifically kills the tumor cells. Combination of hyperthermia with radiation results in a significant increased release of HMGB1 and HSP70 and consecutive activation of DCs [24,29,30]. Additionally, immunogenic cell death forms such as necroptosis, a programmed form of necrosis, might also get induced [31]. The activation of innate and adaptive immune responses against the tumor by the hyperthermia induced released HSP70 is summarized in Fig. 1.

Besides inducing immunogenic cancer cell death, hyperthermia might also directly activate immune cells present in the tumor and its microenvironment [32]. Hyperthermia especially improves DC functions during immune activation and has therefore the capability to deliver tumor antigens and to directly activate DCs [33]. This could even lead to a dynamic immunomodulation by hyperthermia in combination with radiotherapy resulting in enhanced tumor regression as has been reported recently in a patient of liposarcoma [34]. Thus, hyperthermia in multimodal tumor therapy settings can be also considered as immune therapy for cancer, mirroring "*in situ* tumor vaccination" [32,35,36]. This supplements the known radio- and chemosensitizing capabilities of hyperthermia.

Hyperthermia delivering technology

The application of clinical hyperthermia can be either divided as a whole-body, regional or local. The heating techniques are often characterized as superficial or deep (>4 cm from the skin surface)

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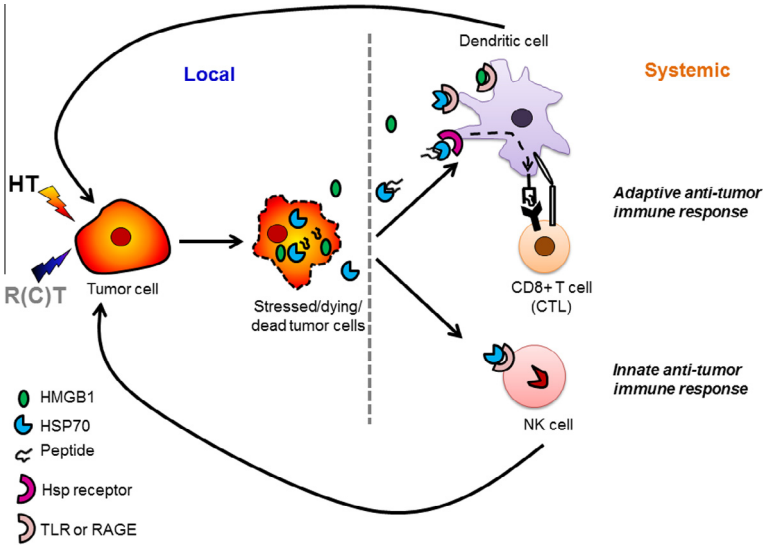

Fig. 1. Multiple biological and immunological anti-tumor modes of action of hyperthermia. Besides being a potent radio- and chemosensitizer, hyperthermia further sensitizes cancer stem cells and might generate in combination with radio- and or chemotherapy an *in situ* vaccine. The related mechanism is based in part on the release of heat shock proteins and other dangers signals such as HMGB1 by the heated tumor cells. HSP70 e.g. chaperons tumor peptides and delivers them to dendritic cells (DCs) via binding to HSP receptors. DCs then processes the tumor peptides and cross-present the respective potential tumor antigens via MHC class I molecules to CD8+ T cells (cytotoxic T cells, CTLs) with appropriate co-stimulation. HMGB1 binds directly to DCs via toll like receptors (TLRs) or RAGE (receptor for advanced glycation end products) and thereby fosters the cross-presentation of these antigens. Additionally, danger signals might directly active natural killer (NK) cells as part of the innate immune system. Finally the tumor cells are lysed by NK cells and CTLs.

or as external and internal (invasive or intraluminal) [6]. The mechanisms to induce hyperthermia include thermal conduction using a circulating liquid and exposure by electromagnetic (radiofrequency, microwaves or infrared) or acoustic waves (ultrasound). In radiative electromagnetic and ultrasound hyperthermia, interference of waves is exploited to enable heating of deeply located target regions and focus the heat to a predefined target volume. In the current clinical practice of hyperthermia, state-of-the-art is external hyperthermia using radiative electromagnetic waves.

Clinical outcomes using loco-regional hyperthermia with radiotherapy and-/or chemotherapy

Taking into consideration the encouraging evidences from various *in vitro* and *in vivo* studies on the biological basis of interaction of hyperthermia with radiotherapy and/or chemotherapy, a number of clinical studies have been reported in a wide range of tumor sites. A MEDLINE® search was conducted on December 20, 2014, using the terms "hyperthermia NOT fever AND cancer AND clinical trials" to look for the comparative studies (both randomized and nonrandomized) reporting outcomes in terms of the complete tumor response at the end of treatment. The treatment assigned could be radiotherapy or chemotherapy versus hyperthermia in addition to radiotherapy or chemotherapy. In many of these trials, hyperthermia was used for previously treated recurrent tumors.

As reporting on survival outcomes were variable, we looked primarily at the complete regression rates achieved following treatment as evaluated clinically, radiologically or histopathologically in these tumor sites. Thus, excluding some of the reports which were updated in a subsequent publication or duplicate reports, 44 of the 518 citations were studies that compared radiotherapy (± chemotherapy) versus thermoradiotherapy (± chemotherapy). The outcomes of these studies along with other studies with chemotherapy and hyperthermia are detailed below.

Radiotherapy vs. radiotherapy and hyperthermia

The clinical outcomes from 38 clinical trials in terms of achieving complete responses with radiotherapy vs. thermoradiotherapy in various tumor sites, namely – breast, cervix, head and neck, rectum, urinary bladder, esophagus, lung, skin melanoma, choroidal melanoma, anal canal and others are summarized in Table 1 [10,12,37–66]. A total of 1717 patients were reported to be treated with radiotherapy alone while 1761 patients with radiotherapy and hyperthermia. An overall complete response of 39.8% with radiotherapy and 54.9% with thermoradiotherapy (odds ratio: 2.3, 95% confidence interval 1.95–2.72, $p < 0.001$) was achieved. Cancers of the breast, cervix, head neck, rectum, urinary bladder, esophagus, cutaneous melanoma and choroidal melanomas were the common sites where radiotherapy was evaluated against thermoradiotherapy. These sites all demonstrated a significant benefit with addition of hyperthermia. The individual and the combined outcomes of each site are presented in Table 1.

Toxicity profiles with hyperthermia were also checked in these studies. Significant increase in acute or late toxicity with addition of hyperthermia to radiotherapy was not evident from these studies. However, the exact quantification of the toxicities was not possible, as the criteria for definition of toxicity varied in these 38 studies reported over a period of 27 years (1987–2014).

In addition, to the above 38 trials listed in Table 1, six studies of interest which could not be included as the complete response following treatment was not stated, are briefly summarized below.

Vasanthan et al. reported a multi-centric randomized trial in 110 patients of FIGO stages IIB–IVA, treated either with radiotherapy or thermoradiotherapy [67]. They reported no benefit in local control or survival with addition of hyperthermia to radiotherapy. It may be noted that of their five participating centers, one did not have any hyperthermia treatment facility while no details of the hyperthermia equipment were mentioned for two other centers. The deficiencies of this trial included suboptimal radiotherapy, inadequate hyperthermia treatment delivery and quality control and the inadequate sample size [68]. This makes it difficult to interpret the true validity of the conclusions, as an advantage with thermoradiotherapy was evident from combined outcome of six trials in similar stages of cancer cervix (odds ratio: 2.19, 95% confidence interval 1.45–3.32, $p < 0.001$, Table 1).

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Table 1
Summary of complete local tumor control reported by randomized or nonrandomized two arm clinical studies for various tumor sites with radiotherapy (± chemotherapy) versus radiotherapy (± chemotherapy) and loco-regional hyperthermia.

Site	Author, year	Patient characteristics	Treatment offered		CR/total		End point	Odds ratio (95% CI)	*p* value
			RT	RT + HT	RT	RT + HT			
Complete local response in breast: RT (88/181, 48.6%) vs. RT + HT (122/198, 61.6%), Odds ratio = 2.10 (95% CI, 1.34–3.30), $p = 0.001$									
Breast	Vernon et al., (DHG), 1996 [37]	Pre-irradiated, recurrent	RT	RT + SHT	14/19	14/19	CR	1.00 (0.24, 4.24)	1.000
Breast	Vernon et al., (MRC BrR), 1996 [37]	Pre-irradiated, recurrent	RT	RT + SHT	17/59	51/90	CR	3.23 (1.60, 6.51)	0.001
Breast	Vernon et al., (MRC BrI), 1996 [37]	Locally advanced	RT	RT + SHT	8/12	10/18	CR	0.63 (0.14, 2.85)	0.544
Breast	Vernon et al., (ESHO), 1996 [37]	Pre-irradiated, recurrent	RT	RT + SHT	11/29	21/27	CR	5.73 (1.76, 18.59)	0.004
Breast	Vernon et al., (PMH), 1996 [37]	Pre-irradiated, recurrent	RT	RT + SHT	5/16	5/17	CR	0.92 (0.21, 4.05)	0.909
Breast	Masunaga et al., 1990 [38]	Locally advanced/recurrent	RT	RT + SHT/DHT	33/46	21/27	CR + PR (>80%)	1.38 (0.45, 4.19)	0.571
Complete local response in cervix: RT (173/263, 65.7%) vs. RT + HT (200/251, 79.6%), Odds ratio = 2.19 (95% CI, 1.45–3.32), $p < 0.001$									
Cervix	Zolciak-Siwinska et al., 2013 [39]	FIGO II–III	ICRT	ICRT + ISHT	91/109	84/96	LC	1.38 (0.63, 3.05)	0.418
Cervix	Franckena et al., 2008 [40]	FIGO IIB–IVA	RT + ICRT	RT + ICRT + DHT	32/56	48/58	CR	3.60 (1.52, 8.53)	0.004
Cervix	Harima et al., 2001[41]	FIGO IIIB	RT + ICRT	RT + ICRT + DHT	10/20	16/20	CR	4.00 (0.98, 16.27)	0.053
Cervix	Sharma et al., 1991 [42]	FIGO IIA–IIIB	RT + ICRT	RT + ICRT + DHT + ICHT	11/22	14/20	LC	2.33 (0.66, 8.31)	0.191
Cervix	Datta et al., 1987 [43]	FIGO IIIB	RT + ICRT	RT + ICRT + DHT	15/26	20/27	CR	2.10(0.66, 0.69)	0.211
Cervix	Chen et al., 1997 [44]	FIGO IIB, IIIB	RT + ICBT	RT + ICBT + DHT	14/30	18/30	CR	1.71 (0.62, 4.77)	0.302
Complete local response in head & neck: RT (183/364, 50.3%) vs. RT + HT (266/353, 75.3%), Odds ratio = 3.71 (95% CI, 2.55–5.38), $p < 0.001$									
Head neck	Wen et al., 2014 [45]	NP (TNM II–IVA)	RT	RT + ICHT	23/49	34/49	rCR	2.56 (1.12, 5.86)	0.026
Head neck	Kang et al., 2013 [46]	NP (TNM III–IV)	CTRT	CTRT + ICHT	49/78	62/76	CR	2.62 (1.25, 5.49)	0.011
Head neck	Hua et al., 2011 [47]	NP (TNM I–IV)	RT	RT + ICHT	73/90	86/90	rCR	5.01 (1.61, 15.55)	0.005
Head neck	Huilgol et al., 2010 [48]	OC, OP, HP (TNM II–IV)	RT	RT + HT	11/26	22/28	CR	5.00 (1.52, 16.46)	0.008
Head neck	Hiraki et al., 1998 (Radical RT) [49]	OP, HP	RT	RT + HT	4/15	11/15	CR	7.56 (1.50, 38.15)	0.014
Head neck	Hiraki et al., 1998 (Preop RT) [49]	OP, HP	Preop RT	Preop RT + HT	4/24	10/18	pCR	6.25 (1.51, 25.86)	0.011
Head neck	Valdagni et al., 1994 [50]	Neck nodes	RT	RT + HT	9/22	15/18	CR	7.22 (1.61, 32.46)	0.010
Head neck	Svetitsky PV, 1990 [51]	Recurrent laryngeal cancers	CT + RT	CT + RT + HT	0/28	8/26	CR	26.19 (1.42, 481.51)	0.028
Head neck	Datta et al., 1990 [52]	OC, OP (I–IV)	RT	RT + HT	10/32	18/33	CR	2.64 (0.96, 7.28)	0.061
Complete local response in rectum: RT (16/205, 7.8%) vs. RT + HT (36/208, 17.3%), Odds ratio = 2.15 (95% CI, 1.10–4.20), $p = 0.025$									
Rectum	van der Zee et al., 2000 [53]	Variable/recurrent	RT	RT + HT	11/71	15/72	CR	1.44 (0.61, 3.39)	0.409
Rectum	Trotter et al., 1996 [54]	Recurrent/primary unresectable	RT	RT + HT	2/37	2/36	CR	1.03 (0.14, 7.73)	0.978
Rectum	You et al., 1993 [55]	Preoperative	Preop RT	Preop RT + ICHT	2/38	10/44	CR	5.29 (1.08, 25.93)	0.040
Rectum	Berdov et al., 1990 [56]	T4 N0 M0	RT	RT + HT	1/59	9/56	CR	11.11 (1.36, 90.83)	0.025
Complete local response in urinary bladder: RT (35/86, 40.6%) vs. RT + HT (69/118, 58.4%), (Odds ratio = 2.40 (95% CI, 1.25–4.62), $p = 0.009$									
Ur. Bladder	van der Zee et al., 2000 [53]	T2–4, N0–1	RT	RT + HT	25/49	38/52	CR	2.61 (1.14, 5.98)	0.024
Ur. Bladder	Masunaga et al., 1994 [57]	T1–4 N0 M0	Preop RT	Preop RT + HT	10/21	16/28	pCR	1.47 (0.47, 4.57)	0.509
Ur. Bladder	Matsui et al., 1991 [58]	T2–4	RT	RT + IVHT with BLM	0/16	15/38	CR	21.77 (1.21, 389.95)	0.036
Complete local response in esophagus: RT (24/132, 18.2%) vs. RT + HT (47/162, 29%), Odds ratio = 2.64 (95% CI, 1.34–5.20), $p = 0.005$									
Oesophagus	Nozoe et al., 1995 [59]	TNM I–IV	Preop RT	Preop RT + CT + HT	15/25	21/26	LC	2.80 (0.79, 9.89)	0.110
Oesophagus	Kuwano et al., 1995 [60]	TNM I–IV	Preop CTRT	Preop CTRT + HT	9/107	26/136	pCR	2.57 (1.15, 5.76)	0.021
Complete local response in lung: RT (2/70, 2.8%) vs. RT + HT (7/59, 11.8%), Odds ratio = 2.69 (95% CI, 0.51–14.22), $p = 0.243$									
Lung	Mitsumori et al., 2007 [61]	NSCLC (IIB–IIIB)	RT	RT + HT	2/40	2/40	rCR	1.00 (0.13, 7.47)	1.000
Lung	Karasawa et al., 1994 [62]	NSCLC (IIIA–B)	RT	RT + HT	0/30	5/19	CR	23.14 (1.20, 447.32)	0.038
Complete local response in superficial tumors: RT (57/169, 33.7%) vs. RT + HT (75/175, 42.8%), Odds ratio = 1.48 (95% CI, 0.94–2.32), $p = 0.091$									
Superficial tumours	Jones et al., 2005 [63]	Primary, recurrent	RT	RT + SHT	22/52	37/56	CR	2.66 (1.22, 5.79)	0.014
Superficial tumours	Perez et al. (RTOG), 1991 [10]	Recurrent, primary, metastatic	RT	RT + SHT	35/117	38/119	CR	1.10 (0.63, 1.91)	0.737
Other sites (Odds ratios given below for each of the site)									
Choroidal melanoma	Yarovoy et al., 2012 [64]	Choroidal melanoma	Ru	Ru + TPHT	20/70	33/63	CR	2.75 (1.34, 5.63)	0.006
Anal canal	Kouloulias et al., 2005 [65]	T2–3 N0 M0	CTRT	CTRT + ICHT	17/25	23/24	LC	10.82 (1.23, 94.92)	0.032
Skin melanoma	Overgaard et al., 1996[66]	Melanoma	RT	RT + HT	23/65	39/63	CR	2.97 (1.45, 6.09)	0.003
Multiple sites	Emami et al., 1996 [12]	Recurrent (head neck, pelvis)	ITRT	ITRT + ITHT	47/87	50/87	CR	1.15 (0.63, 2.09)	0.647
Overall complete local response in all sites: RT (685/1717, 39.8%) vs. RT + HT (967/1761, 54.9%), $I^2 = 28.49$, Odds ratio = 2.30 (95% CI, 1.95–2.72), $p < 0.001$									

RT: radiotherapy, HT: hyperthermia, CR: complete response; rCR: radiological complete response; pCR: pathological complete response; PR: partial response; LC: local control; SHT: superficial hyperthermia, DHT: deep hyperthermia; ICRT: intracavitary radiotherapy; ITRT: interstitial radiotherapy; ITHT: interstitial hyperthermia; IVHT: intravesical hyperthermia; CTRT: chemoradiotherapy; ISHT: interstitial hyperthermia; ICHT: intracavitary hyperthermia; NP: nasopharynx; OC: oral cavity; OP: oropharynx; HP: hypopharynx; NSCLC: non-small cell lung cancers: Ru: ruthenium plaque; TPHT: transpupillary hyperthermia.

Sneed et al. conducted a randomized phase II/III study in 112 patients of glioblastoma multiforme [69]. 39 of their patients received brachytherapy boost while 40 patients were treated with interstitial thermoradiotherapy as boost. Time to tumor progression (TTP) and survival were both significantly better with the addition of interstitial hyperthermia to brachytherapy (brachytherapy alone versus brachytherapy and hyperthermia, TTP: 33 weeks vs. 49 weeks, $p = 0.045$; 2-year survival, 15% vs. 31%, $p = 0.02$, respectively).

A randomized trial in 83 patients of nasopharyngeal cancers reported that thermochemoradiotherapy improved the overall ($p = 0.041$) and disease free survival ($p = 0.048$) along with the quality of life of patients when compared to chemoradiotherapy alone [70].

Shchepotin et al. reported the outcomes of a three arm trial with 293 patients of gastric cancers were randomized to either surgery ($n = 100$), preoperative radiotherapy ($n = 98$) or preoperative radiotherapy and hyperthermia ($n = 95$) [71]. Addition of hyperthermia in the preoperative regime with radiotherapy led to a significant benefit in 3- and 5-year survivals ($p < 0.05$).

Maluta et al. evaluated the efficacy of hyperthermia along with chemoradiotherapy in patients of locally advanced pancreatic cancers [72]. The allocation of the patients into thermoradiochemotherapy ($n = 40$) versus chemoradiotherapy group ($n = 28$) were based on patient preference. A better median overall survival of 15 months compared to 11 months was reported in patients treated additionally with hyperthermia ($p = 0.025$).

A randomized study of 151 patients on the use of combined proton therapy with transpupillary thermotherapy in uveal melanomas was reported by Desjardins et al. [73]. Patients treated with proton and hyperthermia tended to have a greater reduction in tumor dimensions ($p = 0.06$) along with a lower secondary enucleation rate ($p = 0.02$). This is perhaps the only clinical study which has used proton therapy with hyperthermia. A prospective phase II study is presently being conducted with proton thermoradiotherapy in unresectable and recurrent soft tissue sarcomas (ClinicalTrials.gov NCT01904565) [14].

Hyperthermia in addition to radiotherapy has also been shown to be promising in locally advanced prostate cancers. Even though, there have been no randomized or nonrandomized clinical trials in prostate with hyperthermia, encouraging results have been reported in single arm studies with hyperthermia and radiotherapy. Maluta et al. in 144 patients of T2b-4 prostate patients reported a 5 year overall survival and biochemical progression free survival of 87% an 49%, respectively [74]. Similarly, Hurwitz et al. reported a 2 year disease survival of 84% which was significantly higher when compared with 64% observed for a similar group of patients treated under RTOG 92-02 [75]. It is therefore desirable that randomized trials in locally advanced prostate cancers between thermoradiotherapy versus radiotherapy alone be initiated to explore the efficacy of thermoradiotherapy over radiotherapy alone.

Chemotherapy vs. chemotherapy and hyperthermia

Four studies were available that had been carried out to evaluate the efficacy of chemotherapy and loco-regional hyperthermia with chemotherapy alone. These pertain to cancers of the urinary bladder, lung, esophagus and soft tissue sarcoma [76–79].

The long term outcome at more than 10 years following intravesical thermochemotherapy with mitomycin-C versus mitomycin C alone was reported in 83 patients of intermediate/high risk non-muscle invasive bladder cancers by Colombo et al. [76]. The recurrence rate following combined therapy versus was 40% compared to 80% in the mitomycin-C arm. The 10-year disease free survival was 53% with thermochemotherapy while 15% with chemotherapy alone ($p < 0.001$).

Sugimachi et al. reported a randomized trial with preoperative chemotherapy (bleomycin and cisplatin, $n = 20$) alone versus chemotherapy and hyperthermia ($n = 20$) in patients of thoracic esophagus (TNM stages I–IV) [79]. Histopathological evidence of effectiveness of the chemotherapy was scored in terms of the complete absence of any viable tumor cells or in those where more than one-third of the cancer cells were necrosed. The effectiveness of chemotherapy and hyperthermia was evident in 41.2% of the resected specimens of patients treated with the combined therapy compared to just 18.8% treated with chemotherapy alone.

A combination of gemcitabine and cisplatin alone versus hyperthermia along with the same chemotherapy regime was advocated by Shen et al. in 40 patients each of stages IIIB and IV non-small cell lung cancer [77]. They did not observe any significant differences in the response rates between the two groups, although an improvement in quality of life was evident in patients with hyperthermia.

Issels et al. reported a large phase III multicentric European Organization of Research and Treatment of Cancer (EORTC) trial in localized high-risk-soft-tissue sarcoma. 341 patients were randomized either to receive etoposide, ifosphamide and doxorubicin (EIA) along with regional hyperthermia ($n = 169$) or EIA regimen alone ($n = 172$) [78]. Patients were subjected to surgery following neoadjuvant treatment. Postoperative radiotherapy was advocated in nearly 60% of the patients of each group, without any hyperthermia. Postoperatively, all patients received adjuvant EIA or EIA with hyperthermia as per their primary allocation. Local progression or death was evident more in patients on EIA alone compared those EIA and hyperthermia (relative hazard: 0.58, CI: 0.41–0.83, $p = 0.003$). The disease free survival was also better with EIA and hyperthermia (relative hazard: 0.70, CI: 0.54–0.92, $p = 0.011$). These results provided a decisive evidence of thermochemotherapy as an effective and viable therapeutic option for high-risk operable soft-tissue sarcoma.

Although non-randomized, the study reported by Wessalowski et al. using chemotherapy and hyperthermia in 44 patients of refractory or recurrent non-testicular germ-cell tumors in children and adolescents (aged, 7 months to 21 years) needs a special mention [80]. Using a 20% lower cisplatin dosage with hyperthermia, an objective response of 86%, 5-year event free survival of 62% and an overall survival of 72% was achieved. The salvage rate achieved is unmatched for recurrent childhood malignant germ-cell tumors.

Recent advances in hyperthermia treatment planning and execution

Clinical hyperthermia is achieved by exposing tissues to conductive heat sources or nonionizing radiation, like radiofrequency or microwaves. The mass-normalized rate of energy absorption by a biological body following hyperthermia is estimated by the parameter – specific absorption rate (SAR), which is related to the temperature as, SAR = 4186 $c\Delta T/t$, (Watts/kg), where c, is the specific heat in kcal/kg, ΔT, is the temperature rise in °C and t, the exposure time in seconds [81]. The thermal dose is represented as cumulative equivalent minutes (CEM) at a standard targeted treatment temperature of 43 °C obtained within 90% of the tumor volume, CEM 43 °C T_{90} and 10 CEM 43 °C T_{90} is usually considered as the goal of the treatment [82,83].

Technical advances, both in terms of hard and software in the last decade have enabled delivery of a potent and even safer loco-regional hyperthermia. Progress in hyperthermia treatment planning has made pretreatment optimization of treatment quality

Please cite this article in press as: Datta NR et al. Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. Cancer Treat Rev (2015), http://dx.doi.org/10.1016/j.ctrv.2015.05.009

possible by using detailed computed tomography (CT) or magnetic resonance (MR) derived anatomical models. Furthermore, noninvasive online thermometry and simulation guided adaptive hyperthermia have allowed optimization of the most relevant heating parameters real-time during the hyperthermia therapy session. These are briefly discussed in the following sections.

Hyperthermia treatment planning

Hyperthermia treatment planning enables the clinicians and physicists to simulate and visualize the expected temperature distributions within the tumor volume. Various parameters, like position of the applicators and individual setting of power and phase of each channel in multi antenna system allows optimization of the heating patterns. With the help of electromagnetic (EM) and thermal simulation software, these individual settings can be adjusted to conform the heat distribution in a patient to the clinical tumor volume and spare the surrounding healthy tissue. An example for treatment planning simulation software is the commercially available HYPERPLAN (BSD Medical Corp., Salt Lake City, Utah, USA), which has been clinically evaluated [84]. Apart from this, there are other software tools available for treatment planning at the different hyperthermia centers in Europe [85]. The principle of all simulation software is similar and the basic steps in the planning process are described in the following section (Fig. 2).

For individualized hyperthermia treatment planning, the first step consists of acquiring a CT or MRI image with the patient in treatment position, e.g. lying in the treatment hammock (Fig. 2a). Using the image data, a full 3D patient model is created by manual, semi-automatic or automatic segmentation of the different tissue types. Often, only muscle, fat, bone and internal air are distinguished, but recently atlas-based approaches in which organs are discriminated have been reported [85–87]. In addition, the target volume is delineated, which can comprise the clinical target volume (CTV) or only the gross tumor volume (GTV). The segmented patient model and target definition and a 3D model of the hyperthermia applicator are then virtually incorporated to the hyperthermia treatment planning software (Fig. 2b). Following this, the tissue specific electromagnetic (EM) properties are assigned to the individual tissues as the propagation and absorption of the EM waves in tissue and the applicator materials depends on the specific electrical conductivity and permittivity. This allows estimation of the propagation of the EM-waves through the patient body from different antennas using a numerical calculation (finite element, FE or finite difference time domain, FDTD). The superposition of the fields of all antennas results in a distribution of SAR for each point in the patient's body. Using the thermal properties of each tissue type, a heat distribution in the patient can be predicted. By optimizing the amplitude and phase of the up to 12 antennas surrounding the body, a concentration of the heat in a predefined target volume can be achieved while keeping the heat in the healthy tissue in a tolerable range (Fig. 2c). The results of the optimization of amplitude and phase for each antenna, and the patient positioning are then transferred to the hyperthermia treatment unit and applied to the patient during the actual hyperthermia treatment session. Online temperature in the tumor volume and normal structures are monitored during the treatment (Fig. 2d).

Noninvasive thermometry

Lack of adequate heating could have an equivocal impact on the treatment outcomes, as is evident from some reports [10,12,88]. The strongly inhomogenous and dynamic blood flow and tissue perfusion is not accounted for in the presently available commercial hyperthermia treatment planning software. Online temperature assessment is therefore essential for assessment of the temperature distribution in the heated volumes. Use of invasive thermometry is usually restricted to few temperature sensor points within the implanted sites. Moreover, invasive thermometry may not be patient friendly, especially for weekly or biweekly hyperthermia treatments extending over 5–7 weeks. Thus, noninvasive thermometry would be highly desirable for a true and dynamic evaluation of the temperature distribution within the tumor and adjoining normal tissues during the hyperthermia sessions.

Noninvasive thermometry is currently based on the various thermal sensitive magnetic resonance imaging (MRI) parameters [89]. These are primarily (a) proton resonance frequency shift (PRFS) (0.7 Hz per °C at 1.5*T*), (b) diffusion coefficient D (2–3% per °C), (c) longitudinal relaxation time T_1 (≈1% per °C) and (d) equilibrium magnetization M_0 (0.3% per °C). Of all these techniques, the PRFS is the most sensitive proton imaging technique with a resolution of ±0.5 °C. It exhibits a linear relationship between phase shift and temperature shift at a specific magnetic field strength in a wide range of temperature inside water content tissue (except fat and bone). It shows no hysteresis and no dependence to the tissue structure, like necrosis.

The currently commercially available 3D MRI hybrid hyperthermia units allows both MRI and radiofrequency hyperthermia in the same unit and enables real time temperature display on the uncorrected gradient-echo (GRE) images (Fig. 3). Using customized software for MR thermometry, the MRI scans are performed sequentially, starting with the baseline preheating image at specified time period intervals. The consecutive GRE phase images are subtracted from the preceding image and the information on the temperature differences contained in the phase difference image are displayed in color wash with reference to the temperature scale. The anatomic information of the GRE magnitude images is added and following the drift adjustment for the static magnetic field by use of silicon oil references, the temperature distributions on the sectional images are displayed. These temperatures are represented as the increment changes in temperature over their basal values.

Gellermann et al. reported an excellent correlation of the temperatures using PRFS and direct thermometric measurements in a series of patients with soft tissue sarcomas (R^2 = 0.96) [90]. A significant histopathological response, defined as a necrosis of greater than 90% in the tumors and thermal dose at 43 °C to 90% of the target volume (p = 0.05) was observed. Similar observations were also reported in recurrent rectal cancers [91]. Furthermore, although a mean temperature of 42 °C was reached in most tumors volume; higher temperature was observed in necrotic parts of tumors having low perfusion. Craciunescu et al. also reported a correlation of less than 1 °C between MRI based thermal estimates and invasive temperature measurements in high grade soft tissue sarcomas [92].

Overall, the PRFS is considered to be the most appropriate noninvasive thermometry method in motionless regions (pelvis, limbs, etc.). However, it is a challenge for abdominal tumors due to both motion and tissue heterogeneity [88]. Other noninvasive thermometry techniques being evaluated for a possible clinical application include microwave thermal imaging, infrared, ultrasound and CT-based thermometry [93].

Simulation-guided adaptive hyperthermia techniques

Following the advances in accurate 3D patient-specific modeling, adaptive treatment approaches based on electromagnetic and temperature simulations are under development. Most prominently, pretreatment planning is beginning to see use in applications like preplan-assisted real-time treatment guidance.

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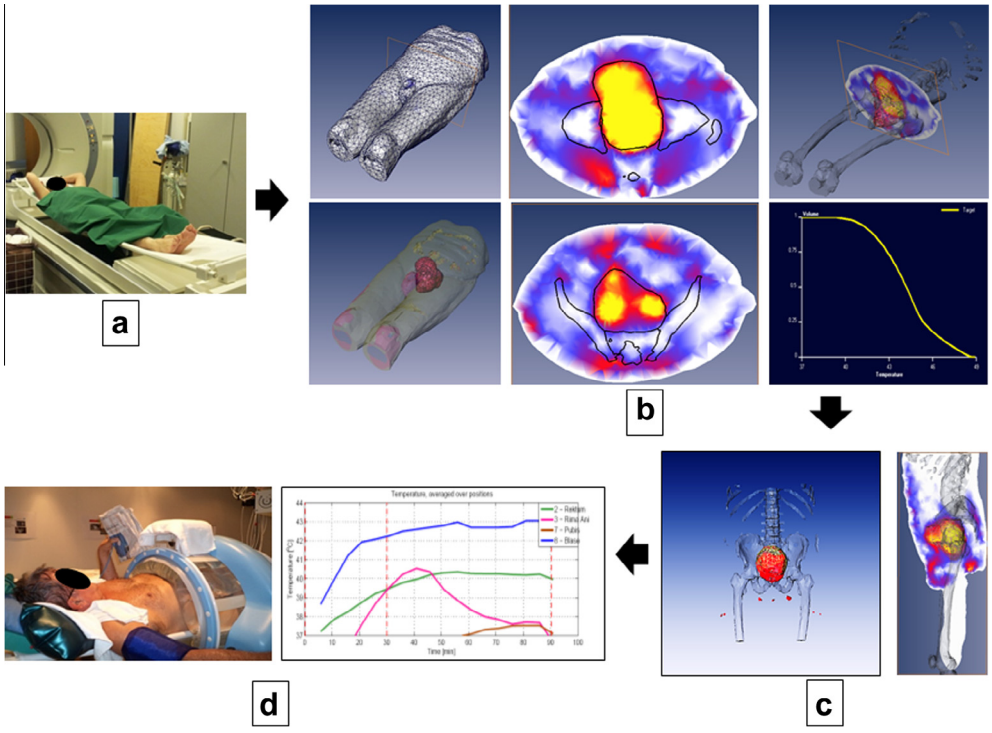

Fig. 2. Flowchart depicting the process of hyperthermia treatment planning in a case of cancer of the urinary bladder (a) Hyperthermia planning CT scan with patient on a hammock, similar to that on the deep hyperthermia treatment unit (b) Segmentation and grid model created for tumor and body tissues with different dielectric properties. Temperature distribution in tissues generated on hyperthermia planning system (HYPERPLAN) are depicted in the volume of interest along with the cumulative thermal dose volume histogram (c) 3D thermal dose distributions in bladder from HYPERPLAN (d) Online temperature recording during treatment with patient undergoing hyperthermia.

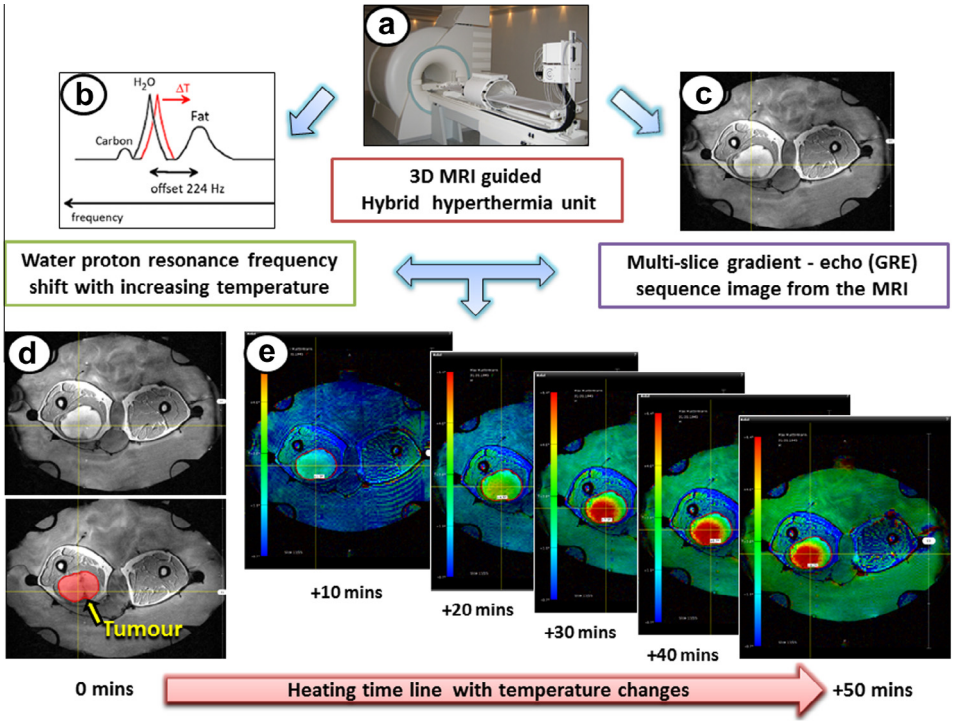

Fig. 3. Noninvasive thermometry during hyperthermia treatment session using (a) 3D MRI hybrid hyperthermia unit. (b) This is based on the proton resonance frequency shift (PRFS) as tissue demonstrates a temperature dependent negative shift of the water PRFS at 1.5*T*. (c and d) The gradient–echo (GRE) images are obtained during the hyperthermia treatment session and the tumor is delineated. (e) Consequent images taken at each 10 min intervals from 0 to 50 min during hyperthermia. Each of the sequential images is subtracted from its predecessor to obtain a color wash image of the temperature distribution which is displayed in color scale. (*Various elements used in this figure have been kindly provided by Dr. Sennewald, BSD Medical Corporation*).

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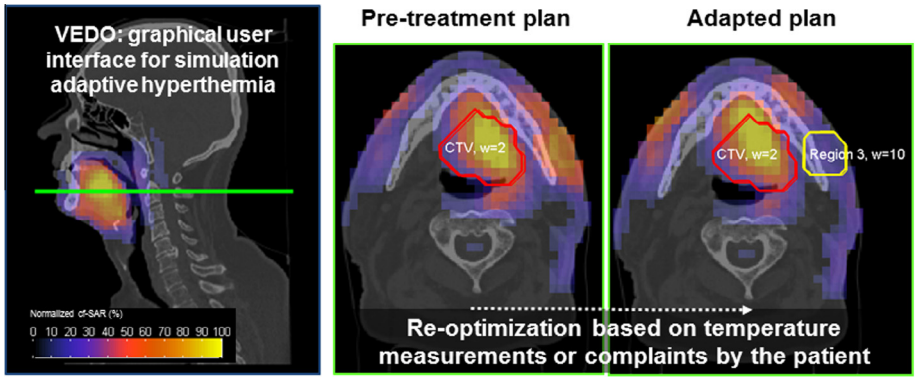

Fig. 4. Simulated power absorption distributions, expressed in the normalized cubic-filtered specific absorption rate (% SAR), displayed on top of the hyperthermia/radiotherapy planning CT scan for "pre-treatment settings" (sagittal and axial view) and "adapted settings" (axial view) as predicted for the HYPERcollar3D. This example shows that the local SAR at the hotspot (region 3, yellow contour) could be reduced by fourfold at the location of the hotspot, while the power delivery to the clinical target volume (CTV, red contour) remained virtually unaffected.

Treatment settings optimized in pretreatment planning could still produce treatment limiting hotspots [94]; strategies are therefore under development to quantify objective or subjective feedback to the treatment planning system for real-time adaptation recalculation of the treatment settings [85]. In this approach, information such as temperature readings from invasive, intraluminal [85,94,95] or non-invasive temperature measurements [90,96,97] and subjective information such as complaints from the patient are combined and used as feedback to derive improved settings [98]. Subsequently, treatment settings are adjusted in real-time to reduce hotspots while retaining or increasing target temperatures by increasing the applied power [99].

Effective use of combining feedback from measured temperatures and complaint-adaptive steering has been documented with clinically evaluated objective measures [100,101]. Recently, VEDO (Visualizer for Electromagnetic Dosimetry and Optimization), a software tool specifically designed to reduce the complexity of SAR-steering has been developed [99] (Fig. 4). By displaying calculated SAR superimposed on CT (or MRI) anatomy during treatment, VEDO provides the operator with insight into the anticipated complex interference patterns between antennas that might contribute to hotspots and patient pain making it easier to correlate patient complaints to actual SAR locations in the treatment plan.

In a randomized trial, complaint-adaptive steering using VEDO allowed inexperienced operators to perform a treatment similar in quality to that from an operator with 20 years' experience with a four-channel Sigma 60 system [101]. Simulation based steering with VEDO is currently being investigated for high frequency systems with more antennas, i.e. the potential for the HYPERcollar3D as shown in Fig. 4 [102]. Early clinical evaluation has demonstrated the utility of this approach.

Real-time adaptive hyperthermia can be improved by fine tuning the patient or applicator models based on measurements during treatment. Adaptation of the 3D patient and applicator (e.g. water bolus-shape) models based on MRI scanning during MR guided hyperthermia is theoretically feasible, but the adaptation combined with re-calculation of the electromagnetic fields per antenna is currently challenging [86,103,104]. Other future real-time simulation improvement options during MR guided hyperthermia include correcting for applicator mismatches [97,105] and-/or imaging the properties per tissue, e.g. using magnetic field mapping to deduce dielectric property maps [106,107] or several MRI techniques to measure perfusion [108].

An alternative method to obtain tissue-specific properties is by iterative parameter reconstruction based on matching temperature simulations with measurements [109]. The potential of this approach was recently evaluated using invasive measurements to reconstruct the patient and temperature dependent-tissue properties [110]. This procedure substantially improved the predictive value of the simulations.

Thus, several techniques have been developed to merge the information from simulations and measurements, in a user-friendly way. This helps operators to improve their insight in the complex thermoregulatory response of individual patients. In addition, simulation guidance objectifies the setting adaptations applied, thereby improving the treatment reproducibility and quality control. Hence, simulation-guided adaptive hyperthermia, especially combined with high resolution (non-invasive) thermometry, provides opportunities for improving the 3D thermal dose delivered to the target while safeguarding the normal tissue thermal dose.

Prospects of combined hyperthermia and radiation planning

Planning the biological effect of hyperthermia is crucial but also challenging as multiple mechanisms contribute to its radiosensitizing effect, including enhanced killing of hypoxic cells and reduced repair of DNA damage caused by radiotherapy [8,111,112]. The thermal enhancement of radiotherapy by hyperthermia is generally quantified using the thermal enhancement ratio (TER), defined as the radiation dose required to obtain a given endpoint with radiation alone relative to the radiation dose needed for the same effect with combined hyperthermia and radiation [113]. TER depends not only on the duration and temperature level during hyperthermia, but also on the order and time interval between hyperthermia and radiotherapy [113]. Choosing an optimal order and time interval between radiotherapy and hyperthermia is important to achieve adequate efficacy while avoiding side effects. A favorable therapeutic ratio between tumor and normal tissue can be achieved when hyperthermia is applied 1–4 h after radiotherapy [113]. Thus, contrary to most anti-cancer treatments hyperthermia, has a low risk of side effects when administered properly.

Integration of hyperthermia and radiotherapy planning requires translation of the radiosensitizing effect into the biological parameters used in radiotherapy treatment planning. A recent study quantified the therapeutic effect of hyperthermic radiosensitization by converting radiotherapy dose distributions with hyperthermia to biologically equivalent radiotherapy dose distributions without hyperthermia for a group of 15 prostate cancer patients [114]. The linear-quadratic model (LQ-model) was used with temperature dependent parameters to express the thermal dose

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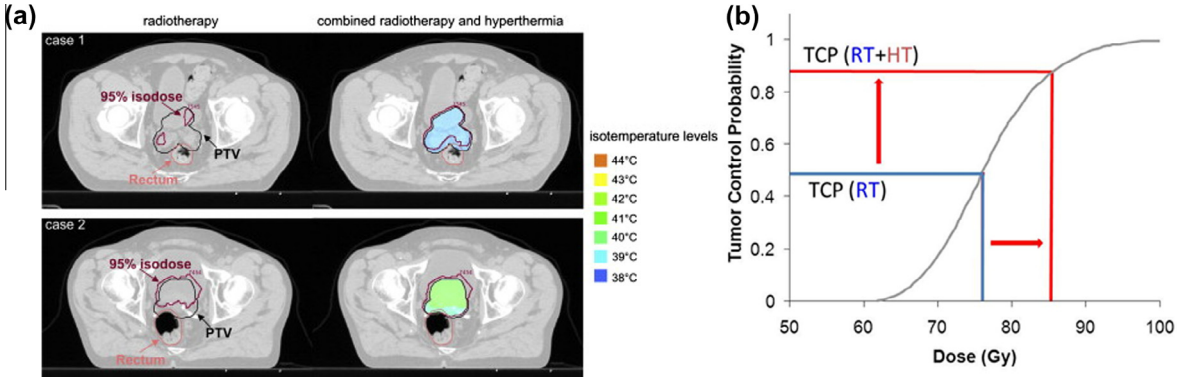

Fig. 5. (a) Example of a treatment planning with dose distributions for radiation therapy alone and equivalent dose distributions for combined radiation therapy and hyperthermia for two different cases with very different dose and temperature distributions. Adding hyperthermia yields an extension of the high-dose region. In this example, the 95% isodose level (i.e., 95% of the dose in the isocenter) is shown. (b) Predicted hyperthermic dose escalation from 76 Gy to 86 Gy [114] results in a rise of the tumor control probability (TCP) from ~50% to ~90% for high risk prostate cancer patients when hyperthermia is added to radiotherapy. TCP curves for high risk prostate cancer patients after Levegrün et al. [121].

dependent radiosensitizing effect, using α and β values at both normothermic and hyperthermic temperatures reported in the literature. This simulation study showed that addition of hyperthermia treatment at a realistic and clinically achievable average median temperature increase of 41.6 °C yielded an average effective radiotherapy dose escalation from 76 Gy to 86 Gy. This would result in a substantial increase in tumor control probability to about 90% for high risk prostate carcinoma patients (Fig. 5).

Conclusions and future prospects

Apart from the various aspects that have been mentioned above, pertaining to thermal radiobiology, thermal immunomodulation and technical developments in hyperthermia hard and software, the future may also see the emergence of nanotechnology based hyperthermia treatment [115]. These are currently under investigation and development and could take some time before they are introduced in routine clinics. With the enhance permeability and retention effect with nanoparticle; these could preferentially accumulate in tumors, enabling selective heating, tumor targeting with thermo-labile liposomal chemotherapeutic agents, theranostics along with local radiotherapy. The thermo-labile liposomal chemotherapeutic agents could help in reducing the generalized toxicity of the chemotherapy drugs by selective drug delivery at the tumour site [116,117]. *In vitro* studies indicate nanoparticle mediated hyperthermia could be effective against the cancer stem cells, which being both radio- and chemoresistant are one of the key decisive factors for tumor cure [118]. Initial clinical trials in glioblastoma multiforme and prostate cancers have been quite encouraging [119,120].

Thus, hyperthermia, as a viable and valuable addendum to the existing therapeutic modalities in cancer has moved a long way since it was used in early clinical trials in 1970s. With the steady developments in thermal biology, its positive interaction with radiotherapy and chemotherapy, a possible immunomodulatory effect; the biological rationale for its clinical application is quite strong and deserves a relook. Alongside, the rapid strides in the technology have enabled hyperthermia to be practiced with more certainty during actual treatments, and ensure a safer and more effective treatment without any significant additional morbidity.

Contributors

N.R. Datta conceived the paper and contributed to the drafting of the manuscript, literature search, clinical results, compilation and data acquisition, analysis and final editing. S.G. Ordóñez, E. Puric and S. Bodis contributed to the literature search, analysis, evaluation and compilation of the clinical results. The following authors contributed to specific sections of the manuscript – U.S. Gaipl on immune modulation induced by hyperthermia, D. Marder and M.M. Paulides on hyperthermia treatment planning, J. Gellermann on noninvasive thermometry, M.M. Paulides on simulation guided adaptive hyperthermia techniques and H. Crezee on combined radiotherapy and hyperthermia planning. All authors have critically reviewed the intellectual content of the paper and approved the final submitted version.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgements

The authors thank Dr. Sennewald for providing some of the elements used in the illustration of Fig. 3. The study has been supported by the partial Grant from Research Council, Kantonsspital Aarau (Forschungsrat KSA) to N.R. Datta.

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