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Review

Therapeutic hyperthermia: The old, the new, and the upcoming

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ABSTRACT

Hyperthermia has long been used for cancer treatment, either alone or in combination with chemotherapy, radiation therapy, or both. Its efficacy and versatility continue to be well demonstrated in randomized trials across a number of primary cancers, but barriers to its widespread adoption persist including effective delivery and verification systems. This article describes hyperthermia, details its biological mechanisms of action and immunological effects, and summarizes select preclinical data and key clinical trials combining hyperthermia with standard cancer treatments. Current challenges and emerging technologies that have the potential to make this translational therapy more accessible to a greater number of patients are also described.

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Abbreviations: EBRT, external beam radiation therapy; HT, hyperthermia; EIA, etoposide, ifosfamide, and doxorubicin; pCR, pathologic complete response rate; MMC, mitomycin C.

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1. Background

Hyperthermia therapy (HT) refers to the treatment of disease through heating and has been used in various forms since the time of the ancient Egyptians (Seegenschmiedt, 1995). Although it can be used alone, HT is most often used in combination with other therapeutic modalities including chemotherapy (CT) and radiation therapy (RT) (Halperin et al., 2008). For the purposes of this review, we will discuss HT as it relates to cancer treatment.

HT typically falls under three categories: local, regional, or whole-body (Van et al., 2002). Local HT is generally used for solid, localized disease at or near the surface of skin or natural body orifices and can be achieved with external or internal energy sources. Regional HT is generally used for disease in deeper tissues or when a larger area of treatment is required (e.g., locally advanced disease). Regional HT can be achieved by increased perfusion of organs or limbs through heating of the blood or by irrigation of body cavities or through other non-invasive methods such as radiofrequency (RF). Whole body hyperthermia is typically used to treat metastatic disease. The most common approach to whole body hyperthermia is the use of a flexible infra-red chamber. Other methods may involve simply heating a patient's room or wrapping the patient in heated blankets (Van et al., 2002).

In addition to these simple ambient methods of inducing hyperthermia, more complex techniques have been developed that use infrared, RF, microwave, and ultrasound (Habash et al., 2011). Arguably, the greater challenge, however, has been the development of methods to detect the temperatures induced and maintained during HT. Early methods of thermometry were invasive, cumbersome, and often clinically impractical (Gunderson and Tepper, 2007). These issues have been a rate-limiting challenge of more widespread clinical adoption of HT in cancer therapy.

2. Mechanisms of action of hyperthermia

Despite decades of research, the exact mechanism of direct HT-induced cell death is not well understood, but it is felt to be a combination of both heat-induced necrosis and of protein inactivation (e.g., repair enzymes) as opposed to DNA damage (the chief mechanism for radiation-induced cell death) (Lepock et al., 1990; Jorritsma et al., 1986). Other effects of HT have been identified, such as alterations in tumor cytoskeletal and membrane structures, which disrupt cell motility and intracellular signal transduction (Pratt et al., 1999; Liang and MacRae, 1997).

A common explanation for HT-enhancement of RT and CT involves inhibition of homologous recombination repair of double-strand DNA breaks, preventing cells from repairing sub-lethal damage (Bolomey et al., 1995). This view is supported by the fact that adding heat to RT generally does not result in more initial DNA breaks (Warters et al., 1982; Jorritsma and Konings, 1983), but it does appear to inhibit rejoining of RT-induced DNA breaks more than is commonly observed after RT alone (Jorritsma and Konings, 1983; Mills and Meyn, 1983; Dikomey and Franzke, 1992). Krawczyk et al. (2011) provided more recent evidence that HT is responsible for inhibiting important DNA double-strand break repair mechanisms.

HT damages cells and enhances RT and CT sensitivity as a function of both temperature and duration of treatment. In general, as temperature or duration increase, the rate of cell killing also increases. For short treatments of well-vascularized tissue at moderate temperature (<42 °C), HT can increase perfusion to tumors, making them more susceptible to RT and increasing cell-killing (Halperin et al., 2008). This effect is further amplified by the inactivation of enzymes involved in aerobic metabolism, which decreases oxygen consumption and further enhance tumor oxygenation (Oleson, 1995). At temperatures above 42 °C, tumor vasculature is damaged, resulting in decreased blood flow. This HT-induced hemostasis leads to tumor cells becoming hypoxic and acidic. Due to their nutritionally deprived, acidic, and hypoxic environment, it is theorized that a high proportion of tumor cells exist out of cycle. This is thought to add to another complementary effect of RT and HT, as sensitivity of cells to ionizing radiation is influenced by their phase in the cell cycle. Cells in G_0 and S phase are less sensitive to damage from RT, but they show enhanced sensitivity to HT (Gunderson and Tepper, 2007). Therefore, it is not appropriate to view HT as simply a way to deliver more oxygen to a tumor in order to potentiate RT. Rather, it is a much more complex process that involves multiple mechanisms (Song, 1984; Vaupel et al., 1989).

Cancer cells are particularly vulnerable to heating; in vivo studies have shown that temperatures in the range of 40–44 °C cause more selective damage to tumor cells (Van et al., 2002). One major factor in the difference in HT sensitivity between normal and cancerous cells is thought to be explained by basic physiological differences between cancerous and normal tissue vasculature. Normal vasculature is hierarchically assembled into efficient networks of arteries, capillaries, and veins, whereas cancerous blood vessels are chaotic, leaky, and inefficient (Shchors and Evan, 2007). This abnormal vasculature results in poor tumor perfusion, resulting in a hypoxic environment that limits efficacy of traditional RT and results in poor CT penetration into tumor tissue (Van et al., 2002). Other mechanisms by which HT leads to a selective cytotoxic effect on tumor cells include inhibition of key cancer cell-signaling pathways such as AKT, inducing apoptosis, suppression of cancer stem cell proliferation, and others (Man et al., 2015).

3. Immunological effects of hyperthermia

Given that heat shock proteins (HSPs) were initially linked with heat tolerance, hyperthermia was long thought to suppress the immune system by inducing tolerance (Frey et al., 2012). However, later studies demonstrated an increase in immunological attacks against tumors after HT, which were believed to be achieved through activation of HSPs and subsequent modulation of the innate and adaptive immune responses against tumor cells. Although the role of HSPs is still under investigation, these and other studies provided compelling evidence that HT does lead to activation of the immune system and HSP-induced cell death through modification of the tumor cell surface (Frey et al., 2012; Ostberg et al., 2003; Menoret et al., 2002; Manjili et al., 2002; Multhoff, 2009).

While sufficiently high heating will result in protein denaturation, milder heating only results in protein inactivation. Yet by turning off key intracellular enzymes, moderate HT leads to increased expression of HSPs and higher levels of intracellular tumor antigens. The so-called 'second hit' of RT leads to necrotic cell death and release of HSPs and tumor antigens in complexes. HSPs are also actively released from exosomes (Toraya-Brown and Fiering, 2014; Mace et al., 2012; Kaur et al., 2011). These HSPs and tumor antigens are taken up by dendritic cells and macrophages and go on to induce specific anti-tumor immunity (Frey et al., 2012). In this way, local HT application can actually lead to systemic tumor killing. HT has also been shown to benefit induction of therapeutic genes in gene therapy as well as increase the efficacy of various drugs and antibodies (Gunderson and Tepper, 2007).

Aside from its action through HSPs, HT can amplify the immune response against tumor cells in a variety of ways. In vivo studies demonstrate HT-enhancement of NK cell activity, and HT has been shown to increase neutrophilic granulocytes with anti-tumor activity. The adaptive immune system is similarly affected. In vitro

studies show increased T- and, especially, B-cell heat damage, but in vivo these immune cells recover shortly after treatment, interact with HT-induced dendritic cells, and can even proliferate beyond pre-treatment levels due to brief heat-induced lymphopenia. Thus, it has become increasingly clear that HT results in immune stimulation, through both direct heat-mediated cell killing as well as innate and adaptive immune system modulation. Yet, it is important to note that HT's ability to stimulate the immune system is not responsible for its benefits when used as an adjunct to RT. Lymphocytic infiltration does not occur in solid tumors treated with both RT and HT. Rather, the only immune cells present in significant quantities are macrophages responsible for consuming apoptotic and necrotic cellular remnants (Frey et al., 2012).

4. Factors in effectiveness of hyperthermia

Many variables influence the mechanism and degree of cell damage from HT. One key factor is the exposure temperature. Heating cancerous tissue to very high temperatures (above 50 °C) causes protein denaturation and direct ablation of tumor. The term hyperthermia is used in this review to refer to heating within the clinically accepted range of 40–45 °C.

Exposure time is also a major influence on the efficacy of HT. For example, at temperatures above 42.5–43 °C the exposure time can be halved with each 1 °C increase while maintaining equivalent cell killing (Field and Hand, 1990). Given the effectiveness of hyperthermia increases with intensity and duration of treatment, it follows that increasing the rate of heating will also increase tumor killing. In fact, in vitro and in vivo studies have demonstrated that more rapid thermal increases induce greater cell damage (Herman et al., 1981). In a 2012 in vitro study, HT was shown to cause more cell membrane damage when cells were heated more rapidly from 37 to 43 °C. Rapid heating at 50 °C for 30 min resulted in cell death by necrosis, whereas gradual heating at 43 °C for 1 h worked through an apoptotic pathway. While this study focused on increasing the rate of HT to potentiate CT treatments, results obtained from cells treated with HT alone suggests the tumor killing effects of HT can be complementary by both CT and RT. Specifically, lower thermal doses could be used by increasing the rate of heat transfer (Tang and McGoron, 2013).

5. Clinical use of hyperthermia

HT has been delivered by various methods and in conjunction with numerous agents for a variety of illnesses over several decades. HT has shown effectiveness in treating a wide range of tumors, including tumors of the head and neck, breast, brain, bladder, cervix, rectum, lung, esophagus, vulva and vagina, as well as non-melanoma and melanoma skin cancer (Van et al., 2002) and sarcoma (Gillette et al., 1992; Issels et al., 2010; Leopold et al., 1989; Matsuda, 1993; De et al., 2012). Like other forms of cancer treatment, normal tissue tolerances vary for HT, and different disease sites require specific thermal doses. CNS tissues are particularly sensitive, showing irreversible damage from treatments longer than 40 min at temperatures of 42–42.5°. However, most other normal tissues show little to no permanent damage with 1 h of treatment up to 44 °C (Field and Hand, 1990).

An important purpose for applying HT to RT treatments is for management of subclinical disease (Varma et al., 2012). For areas of tissue that have not been previously irradiated, micro-metastases usually resemble normal tissue physiologically and, therefore, have adequate oxygenation. These normoxic micro-metastases also benefit from HT through a mechanism thought to be heat-induced radiosensitization. HT may be used immediately before, during, or after RT to amplify its effects (Johnson et al., 1979); however, this method is more sensitive to timing. For optimal efficacy, HT should be applied simultaneously with RT and given midway through the treatment. Recent research demonstrates such methods are feasible and well-tolerated in patients with locally advanced breast cancer (Varma et al., 2012).

Several phase III trials exploring HT with RT have been performed since the 1980s and are summarized in Table 1. These are discussed below, along with other trials including key retrospective studies and phase II trials. HT in combination with RT often demonstrated no significant increase in treatment-related toxicity beyond what is seen from RT alone (Van et al., 2002).

5.1. Hyperthermia and breast cancer

HT is perhaps best known for its role in the treatment of breast cancer. An international group combined 5 trials started between 1988 and 1991 to study the effect of HT on advanced primary and recurrent breast cancer. These studies were limited to cases where RT was indicated in the primary or recurrent setting and heating of the lesion was feasible. The trials were combined due to slow recruitment. Patients were randomized to RT + HT vs. RT alone with varying treatment schemes. The overall complete response (CR) rate was 41% for RT alone and 59% for RT + HT ($p < 0.001$). Not surprisingly, the greatest effect was observed in patients with recurrent lesions in previously irradiated areas. Severe late toxicities were reported, including bone necrosis, bone fracture, and brachial plexopathy, however these effects can be associated with radiation injury especially in the re-irradiation setting (Vernon et al., 1996). Subsequent widespread clinical implementation has not followed, in part due to criticisms of varying entry criteria and treatment schemes between the 5 trials, but also as a result of the lack of widespread technological capability, familiarity with the techniques, and concerns about reimbursement rates for hyperthermia.

A more recent trial from Duke University Medical Center randomized patients between RT and HT + RT for superficial tumors $\leq$3 cm in depth. Tumors were mostly in the breast and chest wall region (64%), but also included head and neck (13%), melanomas (10%), and other regions (12%). HT was achieved using a microwave spiral strip applicator. This trial differed from other HT clinical trials in that all patients received a test dose prior to randomization in order to determine the feasibility of heating. In all, 109 patients were randomized after 13 patients were excluded based on the results of their hyperthermia test dose. The CR rate was 66.1% with HT and 42.3% with RT alone ($p = 0.02$), with patients receiving HT also having more durable local control ($p = 0.02$). Once again, previously irradiated patients had the greatest incremental gain in LC and CR with HT, showing CR rates of 23.5% for RT alone versus 68.2% for HT + RT for previously irradiated patients vs. 51% and 65%, respectively, for patients without prior RT (Jones et al., 2005).

5.2. Hyperthermia and cervical cancer

The "Dutch Deep Hyperthermia Trial" compared RT + HT to RT alone for 363 patients with locally advanced pelvic tumors including bladder, rectal, and cervical cancers. From 1990–1996, 114 patients with cervical cancers were randomized to a median dose of 68 Gy alone or in combination with HT given once weekly during treatments. At 12-year follow-up, local control (LC) remained better with RT + HT (56% vs. 37%; $p = 0.01$). Survival was also better with RT + HT (37% vs. 20%, $p = 0.03$) and RT toxicity was not enhanced by HT (Franckena et al., 2008). This trial also demonstrated cost effectiveness of HT; the cost per year of life gained was calculated to be only €3956 (~$5277 USD) (Franckena, 2012). A criticism of this trial is that after the trial was well underway, other studies revealed the benefits of cisplatin-based CT, so it is unknown how

Table 1
Phase III trials evaluating adjuvant hyperthermia therapy.

First author (Year)	Site	# Pts	Arms	Local Control	Overall survival
Van der Zee (2002)	Cervix	56	48.3 Gy EBRT + 18 Gy brachy boost	37% (12 yr)	20% (12 yr)
		58	Additional HT 1x/week	56% (12 yr)	37%(12 yr)
Harima (2001)	Cervix	20	52.2 Gy ERBT + 30 Gy brachy boost	48.5% (3 yr)	48.1%(3 yr)
		20	Additional HT 1×/week	79.7%(3 yr)	58.2%(3 yr)
Vasanthan (2005)	Cervix	55	EBRT + brachy (variable)	68.5%(3 yr)	73.2 (3 yr)
		55	EBRT + brachy + HT 1×/week	No sig. diff.	No sig. diff.
Vernon (1996)	Breast	135	EBRT (variable)	69.1%(2 yr)	41%(2 yr)
		171	EBRT + HT	83.2%(2 yr)	36%(2 yr)
(2011)	Bladder	41	MMC	Outcomes were 10-year KM estimated DFS (52.8%vs. 14.6%in the control group)	
		42	MMC + HT		
Van der Zee (2002)	Bladder	49	EBRT	33%	22%
		52	EBRT + HT	42%	28%
Jones (2005)	Superficial sites	52	No HT (mean 41 Gy)	25%	~12%(7 yr)
		56	HT	48%	No sig. diff.
Valdagni (1994)	Head & neck metastatic to lymph nodes	22	EBRT	Not reported	0%(5 yr)
		18	EBRT + HT	Not reported	53.5%(5 yr)
Huilgol (2010)	Head & neck (non-metastatic)	26	EBRT	Outcomes were pCR (78.6%vs. 42.4%in the control group) and median survival (241 days vs. 145 days in the control group)	
		28	EBRT + HT		
Sneed (1998)	Intracranial (glioblastoma multiforme)	39	59.4 Gy EBRT + later 60 Gy brachy boost	Not reported	15%(2 yr)
		40	Additional HT (43 °C) with brachy sessions	Not reported	31%(2 yr)
Mitsumori (2006)	Lung (non-small cell)	40	EBRT	Not reported	38.1%(1 yr)
		40	EBRT + HT	Not reported	43.0%(1 yr)
Overgaard (1995)	Skin (melanoma)	65	EBRT (24 Gy or 27 Gy)	28%(2 yr)	19% overall 5-year survival; greater (38%) for patients with controlled disease compared to persistent disease (10%)
		63	Additional HT (43 °C for 60 min)	46%(2 yr)	
Schroeder (2012)	Rectum	45	50.4 Gy EBRT + chemotherapy	This study measured pCR as an outcome: 6.7%in no-HT group vs. 16.4% in HT group.	
		61	Additional HT (minimum 40.5 °C for 60 min)		
Issels (2010)	Soft tissue sarcoma	172	EIA	55%(4 yr)	59%(4 yr)
		169	EIA + regional HT	66%(4 yr)	57%(4 yr)

the addition of HT would influence outcomes in patients receiving chemoradiation (CRT) (Eifel et al., 2004; Rose et al., 1999).

Besides the Dutch trial, several other randomized trials have demonstrated benefits of HT compared to RT alone for cervical cancer. In 2001, Harima et al. reported on 40 patients with FIGO IIIB cervical cancers and found a significant improvement in CR rate and 3-year local relapse free survival: 80% vs. 50% and 80% vs. 49% for RT + HT and RT alone, respectively ($p = 0.048$ for both) (Harima et al., 2001). In 2005, Vasanthan et al. reported the only published negative study to date, a 110-patient randomized trial of HT + RT for locally advanced cervical cancer (Vasanthan et al., 2005). This study was criticized because of the imbalance between tumor volume in the treatment arms, a possibly inadequate hyperthermia dose, and the inadequacy of capacitive heat delivery in patients with thicker subcutaneous fat (Van der Zee et al., 2005).

HT is of special interest in the case of locally advanced cervical cancer with evidence to suggest that HT may be used to improve LC and lower toxicity in a cost-effective way. Additionally, in patients with early stage cervical cancers who cannot undergo platinum-based therapy, consideration should be given for HT delivered concurrently with RT in attempt to enhance treatment outcomes compared with RT alone (Franckena, 2012). In 2010, a Cochrane Database meta-analysis was published from the results of 6 randomized clinical trials exploring the use of hyperthermia in combination with RT for locally advanced cervical cancer. This study revealed a significantly higher complete response rate, reduced local recurrence, and a significantly better OS with the use of combined modality treatment. The use of combined modality treatment was not associated with an increase in grade 3 or higher toxicity. The authors do note, however, that the limited patient numbers and over-representation of FIGO IIIB disease limit conclusions that can be drawn from this report (Lutgens et al., 2010).

5.3. Hyperthermia and lung cancer

HT has also been explored in recent years to treat non-small cell lung cancer (NSCLC). In 2006, Mitsumori et al. reported the results of a multicenter randomized trial of hyperthermia for locally advanced NSCLC. Between 1998 and 2002, 80 patients were randomized to receive either RT alone (66–70 Gy in 2 Gy daily fractions) or RT combined with with hyperthermia using radiofrequency capacitive heating. Although LC and OS were not significantly different between the groups, the 1-year local progression-free survival was significantly better with the additional of HT (67.5% vs. 29.0%, $P = 0.036$). Furthermore, the toxicities seen with the addition of hyperthermia were generally mild with no grade 3 or higher toxicities reported (Mitsumori et al., 2007).

In 2012, Ohguri et al. reported their retrospective study of 33 patients treated with concurrent re-irradiation and regional HT for locally recurrent NSCLC. While re-irradiation had historically been used only for symptomatic palliation, the authors showed that the addition of HT had greater curative potential than re-irradiation alone with acceptable toxicity, especially for recurrences not involving distant metastases or large tumors. The authors reported a median survival of 18 months, which they compared with two prior studies of re-irradiation alone that had median survival times of 7–8 months. Prospective studies are needed to better quantify the benefit of regional HT for lung cancer (Ohguri et al., 2012).

5.4. Hyperthermia and head and neck cancer

Valdagni et al. performed a phase III study looking at HT for patients with advanced locoregional and stage IV squamous cell carcinoma of the head and neck. Between 1985 and 1986, 41 patients with 44 lymph nodes were randomized to RT alone or RT + HT to lymph nodes. The CR rate in lymph nodes at 3 months was higher for RT+HT than RT alone (83% vs. 41%, $p = 0.0164$). A particularly interesting finding of this study was a 5 year overall survival rate of 53.3% in patients treated with RT + HT versus 0% for those treated with RT alone ($p = 0.02$). However, two patients suffered bone necrosis as a late complication in the HT arm (Valdagni and Amichetti, 1994).

A later trial by Huilgol et al. examined the use of RF-induced hyperthermia in patients with non-metastatic head and neck cancer, primarily T3-T4 and N1-N3. Fifty-six patients were randomized to RT alone or RT in combination with hyperthermia. Treatment arms were evenly matched for age, sex, and stage of disease. Patients in both treatment arms were prescribed a dose of 70 Gy in 2 Gy daily fractions over 7 weeks. Patients in the combined therapy arm received HT for 30 min to an average temperature of 42.3 °C. Although median follow-up was less than 1 year, the clinical CR rate was 42.4% with RT alone and 78.6% in the group that received HT ($p < 0.05$) and Kaplan–Meir analysis of survival also showed a significant improvement in favor of combined modality. Importantly, no dose-limiting thermal toxicities were seen (Huilgol et al., 2010).

5.5. Hyperthermia and central nervous system cancers

Between 1990 and 1995, a phase III trial from UCSF was conducted to determine if adjuvant interstitial HT improved survival of patients with gliobastoma multiforma (GBM) undergoing brachytherapy boost after conventional RT. Adults with newly-diagnosed, focal, supratentorial GBM (≤5 cm in diameter) were initially treated with partial brain RT to 59.4 Gy with oral hydroxyurea. Those patients whose tumor was still implantable after RT were randomized to brachytherapy boost with ($n = 40$) or without ($n = 39$) HT for 30 min immediately before and after brachytherapy. The time to progression and survival were significantly longer with HT compared with brachytherapy alone ($p = 0.04$ for both); however, the incidence of grade 3 toxicities were increased in the HT arm (Sneed et al., 1998). Although the results of this trial were promising, the benefits of HT have not been confirmed in the setting of treatment with temozolomide.

5.6. Hyperthermia and melanoma

In 1995, Overgaard et al. published results of 70 patients with metastatic or recurrent melanoma who were randomized to RT to 25–27 Gy in 3 fractions over 8 days alone or RT followed by HT (43 °C for 60 min). The 2-year LC was improved with the addition of HT (28% with RT alone vs. 46% with RT + HT, $p = 0.008$), and the addition of heat was not associated with increased acute or late toxicities (Overgaard et al., 1995).

5.7. Hyperthermia and gastrointestinal cancers

A Cochrane database review by De Haas-Kock et al. (2009) explored concomitant HT and RT for the treatment of locally advanced rectal cancer. Six randomized clinical trials involving 520 patients, published between 1990 and 2007 were included. From the 4 studies that reported OS rates, a combined analysis found the 2-year OS was significantly better in patients who received RT + HT ($p = 0.001$), however this difference was not apparent at longer follow-up periods including 3, 4, and 5 years. A significant higher pathological CR rate was observed in the RTN + HT group ($p = 0.01$). Of the 2 studies that reported on toxicity, no significant differences were observed between the RT and the RT + HT groups (De et al., 2012).

A German study published in 2012 looked at HT effects on pathological complete response (pCR) rates and surgical options of patients with rectal cancer. Between 2007 and 2010, 106 patients with locally advanced rectal cancer received neoadjuvant chemoradiation with or without regional HT. Both groups received 50.4 Gy in 1.8 Gy daily fractions with 5-fluorouracil. The HT group also received concurrent regional HT to a target temperature of 40.5 °C for at least 60 min. On retrospective analysis, Schroeder et al. concluded the pCR rate could be improved by combining regional HT with neoadjuvant chemoradiation. pCR was achieved in 6.7% of patients in the no-HT arm versus 16.4% in the HT arm, and the pCR rate increased to 22.5% in patients receiving at least four HT treatments ($p = 0.043$). The authors also found a benefit to patients with low-lying rectal tumors near the anal verge, with a greater proportion in the HT group becoming eligible for sphincter-sparing surgery (57% vs. 35%, $p = 0.077$) (Schroeder et al., 2012). While these results are promising, pelvic HT has been shown in other studies to also be associated with a higher rate of treatment discontinuation (Schulze et al., 2006; Van et al., 2000). Thus, it is especially important to establish the degree to which HT benefits patients with rectal cancer, and further randomized trials are warranted.

A feasibility study for the use of hyperthermia in esophageal cancer was published by Albregts et al. (2004). Hyperthermia was delivered with 70 MHz applicators arranged around the thorax to deliver a target dose of 41 °C with temperatures monitored at several locations including intraesoophageal at tumor level. From 1999–2002, 31 patients with mainly T3N1 (stage III) tumors of a mean length of 6 cm were included. Combined hyperthermia and chemotherapy (CDDP and etoposide) was given 55 times in 26 patients. Thermal data showed that is was technically feasible to heat the esophagus to prescribed levels. Treatment was well-tolerated with most toxicities being hematologic and one patient with transient, grade 2 sensory neuropathy. Twenty-two patients went on to have surgical resection and there were no reported complications in the post-operative phase that were attributed to neoadjuvant therapy (Albregts et al., 2004).

A recent study from Nishimura et al. explored the use of HT combined with CT for patients with residual or recurrent esophageal cancer after definitive chemoradiation. 11 patients received salvage HT + CT using RF-induced hyperthermia to 42.5–44.0 °C with cisplatin with 5-fluorouracil, an oral fluoropyrimidine and irinotecan. Complete response and stable disease was achieved in 3 and 5 patients, respectively, and symptoms were improved in the remaining 3 patients. The median time of stable disease was 8 months and the median survival time following HT was 12 months. There were no severe adverse events caused by hyperthermia (Nishimura et al., 2015).

A unique phase I study by Bell et al. explored the application of whole body radiotherapy using an infrared radiant heating

device as part of a regimen which included cisplatin, gemcitabine, and INF-α for chemotherapy-resistant metastatic or otherwise advanced solid malignancies. The study was intended as a dose-escalation chemotherapy study. Cancers of many types were included with gastrointestinal primaries accounting for a large percentage. Thirty-seven patients were treated on the protocol which established a maximally tolerated dose of cisplatin of 60 mg/m^2. Complete and partial responses combined were 43% with particularly good responses being observed in patients with high-grade neuroendocrine and pancreatic cancers. This thermochemotherapy regimen also resulted in an improvement in patient-reported quality of life indicators (Bull et al., 2008).

5.8. Hyperthermia and genitourinary cancers

A small, early study from Van Vulpen et al. demonstrated the potential for using HT in combination with RT for the treatment of locally advanced prostate cancer (LAPC). From 1997 to 2001, 26 patients received 5 weekly regional hypertheramia treatments (40.2–40.8 °C) or one interstitial hyperthermia treatment (39.4–41.8 °C) in combination with EBRT as part of a phase I/II study. Although a non-IMRT technique was used and patients were treated to a lower dose than the current standard, biochemical PFS and OS were 70% and 100%, respectively, at 36 months followup and no toxicities higher than grade 2 were reported (Van Vulpen et al., 2004).

Other, larger reports followed the Van Vulpen experience. Maluta et al. reported on 144 patients with LAPC treated with concurrent RT and local HT and androgen deprivation therapy (ADT). Patients received HT in 4 sessions throughout RT. This phase II study demonstrated a 5-year OS of 87% and a 5-year biochemical PFS of 49% with no late grade 3 toxicities and reported no significant side effects except symptoms related to ADT (Maluta et al., 2007). A similar study by Hurwitz et al. explored the use of transrectal ultrasound hyperthermia plus RT with or without ADT for the treatment of LAPC. The median Gleason score was 7 and the median prostate-specific antigen (PSA) level was 13.3 ng/μL. In this study, patients only received 2HT treatments. In all, 37 patients were treated to a mean cumulative equivalent minutes (CEM) T9O 43 °C was 8.4 min. At a mean followup of 70 months, the 7-year overall survival rate was 94% and biochemical PFS was 61%. 2-year DFS, the primary study endpoint, was significantly improved compared with the 4-month ADT arm of RTOG 9202 (84 vs. 64%) (Hurwitz et al., 2011).

The use of HT has also been explored in the treatment of bladder cancer. Colombo et al. presented 10-year outcomes for non-muscle-invasive bladder cancer (NMIBC) treated with thermochemotherapy as part of a randomized trial. Eighty-three patients with NMIBC were treated with transurethral bladder tumor resection (TURBT) followed by either intravesical thermochemotherapy or chemotherapy alone mitomycin-C (MMC). Ten-year DFS for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively ($P < 0.001$). Bladder preservation rates for thermochemotherapy and chemotherapy alone were 86% and 79%, respectively (Colombo et al., 2011). The already discussed "Dutch Deep Hyperthermia Trial" also included patients with locally-advanced bladder cancer. Although OS was improved for the total patient population, the most pronounced benefit was seen for patients treated for cervical cancer as opposed to the other pelvic malignancies (van der Zee et al., 2000). These reports demonstrate the promise of HT as part of a combined modality approach for the treatment of genitourinary malignancies.

5.9. Hyperthermia and sarcoma

The principle of combining HT with RT for sarcomas was first tested in canines at Colorado State University in 1992. Sixty-four dogs with spontaneous soft tissue sarcomas (STS) and no evidence of metastasis were randomized to receive RT alone or RT + HT. The duration of LC was improved with the addition of HT ($p = 0.04$), and the incidence of late complications was not significantly different between treatment arms (Gillette et al., 1992).

A 1989 phase II trial was conducted at Duke University Medical Center to evaluate different HT treatment schedules for stage IIB-IVA STS. Entry criteria specified tumors be potentially amenable to wide local excision. Seventeen patients were treated with preoperative RT + HT, with HT randomized to one versus two treatments per week and stratified with respect to tumor volume and location. HT was given 30–60 min after radiotherapy for 1 h after 42 °C was reached. RT was given daily to a total dose of 50–50.4 Gy in 1.8–2.0 Gy fractions. Surgical excision was performed 1 month after completion of RT + HT, and the effects of treatment were evaluated by histopathologic examination of resected lesions. All 9 patients in the 2HT per week group had extensive changes, versus only 3 of 8 patients in the 1HT per week group. Acute toxicities attributable to HT occurred in 8 patients, with 6 patients in the 2HT per week arm developing mild to moderate complications like blisters, ulcerations, or pain. No severe toxicities were reported (Leopold et al., 1989).

Following this study, several trials sought to further evaluate the role of HT in STS. Between 1997 and 2006, Issells et al. conducted a phase III trial combining CT with HT for patients with localized high-risk STS (≥5 cm, grade 2–3, and deep to the fascia). In all, 341 patients were randomized to receive either neoadjuvant CT consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone, or EIA combined with regional HT and local therapy, which often included RT. Local progression free survival at 2 years was 76% for the HT arm vs. 61% for EIA alone arm ($p = 0.003$). Patients randomized to HT also had improved disease free survival ($p = 0.011$), response rates ($p = 0.002$), and overall survival ($p = 0.038$), however the latter was based on a pre-specified, per-protocol analysis of patients who completed their entire assigned course of treatment. HT did increase leucopenia (grade 3–4, $p = 0.005$) and mild to moderate morbidities that included pain, bolus pressure, and skin burn. Two deaths were attributable to treatment in the combined treatment group and one death was attributable to treatment in the EIA-alone group (Issels et al., 2010).

Marianne et al. evaluated the role of reirradiation and HT to treat radiation-associated sarcomas. Although the study was limited to only 16 patients, most of whom had angiosarcomas, and a wide range of radiation fractionation schemes and HT applications were used, it suggested a high response rate and durable LC with the combination approach (De et al., 2012).

5.10. Hyperthermia and pediatric cancers

The use of hyperthermia has also been applied to pediatric malignancies. Wessalowski et al. reported on an early experience of 10 children with locoregionally recurrent or chemotherapy-refractory extracranial nontesticular germ cell tumors (GCTs). Patients were treated with electromagnetic waves in combination with platinum-based chemotherapy. This regimen was found to have an objective tumor response in 70% of study patients, with a 50% rate of complete response (Wessalowski et al., 1998). In 2013, Wessalowski et al. reported on a larger clinical trial of 44 patients with refractory or recurrent GCTs. In this trial, concurrent chemotherapy included cisplatin, etoposide, and ifosfamide and non-invasive microwave-induced regional deep hyperthermia was given simultaneously. Eighty-six percent of patients had an objective response to treatment with a 46% rate of complete response. Five-year EFS was 62% and 5-year OS was 72%, which the authors note is similar to outcomes seen in patients receiving first-line therapy. Main toxicities seen were neutropenia, thrombocytope-

nia, granulocytopenic fever, and a 11% rate of grade-3 acute renal toxicity (Wessalowski et al., 2013)

6. Future directions of hyperthermia

Although many trials studying a broad range of cancers have shown benefit to the addition of HT, its clinical application and success remains linked to experience with the modality. Recent technological advances seek to reduce operator dependence by delivering accurate and reproducible tissue heating. A number of capacitive and radiative delivery systems are now available for pelvic HT, and with the advent of online 3D HT planning, these systems should allow for more consistent delivery. Established commercial platforms are now seeing increasing clinical application in the US. An example is the BSD-2000 (BSD Medical, Salt Lake City, UT), which was used in many of the trials previously mentioned and was granted FDA approval in 2011 under a humanitarian device exemption for use with RT to treat cervical cancer in patients ineligible to receive chemotherapy. More importantly new systems are incorporating real-time methods of monitoring the treatment temperature with MRI, which has the potential to overcome one of the most significant hurdles in widespread clinical adoption. Recently published quality assurance guidelines (Bruggmoser et al., 2011) and recommendations for clinical practice integration of HT (Colombo et al., 2011) will also help guide and streamline the process.

While new technologies such as high intensity focused ultrasound (HIFU) are increasingly being explored as a means to induce heating, other technologies and agents are being developed to work in conjunction with HT. Microscopic drug-delivery devices such as liposomes that release their contents in response to heating may improve the therapeutic ratio of systemic cancer treatments (Wessalowski et al., 1998). An example of such a drug is ThermoDox, which is a thermoresponsive form of liposomal doxorubicin. The OPTIMA study is a phase III clinical trial currently enrolling participants to investigate the effectiveness of ThermoDox in combination with standardized RF ablation for treating non-resectable hepatocellular carcinoma. The theory is that HT-level heat created during the ablative process should trigger the release of doxorubicin in margins around the site of ablation. ThermoDox is also being investigated for use in a variety of disease sites (liver, pancreas, breast, brain) in combination with HIFU.

7. Conclusions

HT continues to show clinical benefit in combination with RT and CT for a wide range of cancers including breast, gastrointestinal, gynecological, CNS, thoracic, skin, and sarcoma. Despite these benefits, HT has not yet seen widespread use. Major challenges to clinical adoption of HT have been due to problems with real-time non-invasive monitoring of tissues and difficulties efficiently incorporating HT delivery in the clinical workflow. New technologies are being developed in an effort to improve these shortcomings and there is a renewed interest in both commercial development of treatment platforms and in the academic literature, both of which are promising and suggest that this unique method of treating cancer may still have untapped potential.

Authors' contributions

MM: Collected sources and provided substantial writing contribution, created manuscript table

EG: Collected sources and addressed reviewers comments for the second draft of our manuscript

GJ: Collected sources, provided substantial writing contribution

LG: Collected sources, provided substantial writing contribution

CS: Provided substantial writing contribution and created manuscript tables/figures

All authors read and approved the final manuscript.

Implications for practice

Hyperthermia continues to show clinical benefits in randomized trials across a spectrum of malignancies, with generally well-tolerated side effects when administered as multimodality therapy. Hyperthermia contributes direct tumor cell killing and may also enhance the antitumor effects of chemotherapy and radiation therapy. Its widespread adoption has been impeded by technological and delivery barriers that are now being addressed through new commercial solutions. It would serve physicians of all oncological disciplines to stay informed of new developments and consider integrating these promising techniques into their practice.

Conflict of interest

All authors declare that they have no conflict of interest.

References

Albregts, M.C., Hulshof, M.C., Zum Vorda Siva Vording, P.J., et al., 2004. A feasibility study in oesophageal carcinoma using deep loco-regional hyperthermia combined with concurrent chemotherapy followed by surgery. Int. J. Hyperthermia 20 (September (6)), 647–659.

Bolomey, J.C., Seegenschmiedt, M.H., Fessenden, P., Vernon, C.C., 1995. Thermoradiotherapy and Thermochemotherapy. Springer, Berlin, New York.

Bruggmoser, G., Bauchowitz, S., Canters, R., et al., 2011. Quality assurance for clinical studies in regional deep hyperthermia. Strahlentherapie und Onkologie. Organ Der Deutschen Rontgengesellschaft 187 (October (10)), 605–610.

Bull, J.M., Scott, G.L., Strebel, F.R., et al., 2008. Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine, and daily interferon-alpha: a description of a phase I-II protocol. Int. J. Hyperthermia 24 (December (8)), 649–662.

Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M., Engelstein, D., 2011. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). BJU Int. 107 (March (6)), 912–918.

De Haas-Kock, D.F., Buijsen, J., Pijls-Johannesma, M., et al., 2009. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane DB. Syst. Rev. (3), CD006269 <http://www.ncbi.nlm.nih.gov/pubmed/?term=De+Haas-Kock+hyperthermia+rectal>.

De Jong, M.A., Oldenborg, S., Bing Oei, S., et al., 2012. Reirradiation and hyperthermia for radiation-associated sarcoma. Cancer 118 (January (1)), 180–187.

Dikomey, E., Franzke, J., 1992. Effect of heat on induction and repair of DNA strand breaks in X-irradiated CHO cells. Int. J. Radiat. Biol. 61 (February (2)), 221–233.

Eifel, P.J., Winter, K., Morris, M., et al., 2004. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J. Clin. Oncol. 22 (March (5)), 872–880.

Field, S.B., Hand, J.W., 1990. An Introduction to the Practical aspects of Clinical Hyperthermia. Taylor & Francis, London, New York.

Franckena, M., Stalpers, L.J., Koper, P.C., et al., 2008. 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. 70 (March (4)), 1176–1182.

Franckena, M., 2012. Review of radiotherapy and hyperthermia in primary cervical cancer. Int. J. Hyperthermia 28 (6), 543–548.

Frey, B., Weiss, E.M., Rubner, Y., et al., 2012. Old and new facts about hyperthermia-induced modulations of the immune system. Int. J. Hyperthermia 28 (6), 528–542.

Gillette, S.M., Dewhirst, M.W., Gillette, E.L., et al., 1992. Response of canine soft tissue sarcomas to radiation or radiation plus hyperthermia: a randomized phase II study. Int. J. Hyperthermia 8 (May–June (3)), 309–320.

Gunderson, L.L., Tepper, J.E., 2007. Clinical Radiation Oncology, 2nd ed. Elsevier, Churchill Livingstone, Philadelphia, PA.

Habash, R.W., Krewski, D., Bansal, R., Alhafid, H.T., 2011. Principles, applications, risks and benefits of therapeutic hyperthermia. Front Biosci. (Elite Ed.) 3, 1169–1181.

Halperin, E.C., Perez, C.A., Brady, L.W., 2008. Perez and Brady's principles and practice of radiation oncology. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia.

Harima, Y., Nagata, K., Harima, K., Ostapenko, V.V., Tanaka, Y., Sawada, S., 2001. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int. J. Hyperthermia 25 (August (5)), 338–343.
Herman, T.S., Gerner, E.W., Magun, B.E., Stickney, D., Sweets, C.C., White, D.M., 1981. Rate of heating as a determinant of hyperthermic cytotoxicity. Cancer Res. 41 (September (Pt 1)), 3519–3523.
Huilgol, N.G., Gupta, S., Sridhar, C.R., 2010. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: a report of randomized trial. J. Cancer Res. Ther. 6 (October–December (4)), 492–496.
Hurwitz, M.D., Hansen, J.L., Prokopios-Davos, S., et al., 2011. Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer, long-term results from Dana-Farber Cancer Institute study 94-153. Cancer 117 (February (3)), 510–516.
Issels, R.D., Lindner, L.H., Verweij, J., et al., 2010. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol. 11 (June (6)), 561–570.
Johnson, R.J., Subjeck, J.R., Moreau, D.Z., Kowal, H., Yakar, D., 1979. Radiation and hyperthermia. Bull. N. Y. Acad. Med. 55 (December (11)), 1193–1204.
Jones, E.L., Oleson, J.R., Prosnitz, L.R., et al., 2005. Randomized trial of hyperthermia and radiation for superficial tumors. J. Clin. Oncol. 23 (May (13)), 3079–3085.
Jorritsma, J.B., Konings, A.W., 1983. Inhibition of repair of radiation-induced strand breaks by hyperthermia, and its relationship to cell survival after hyperthermia alone. Int. J. Radiat. Biol. Rel. Stud. Phys. Chem. Med. 43 (May (5)), 505–516.
Jorritsma, J.B., Burgman, P., Kampinga, H.H., Konings, A.W., 1986. DNA polymerase activity in heat killing and hyperthermic radiosensitization of mammalian cells as observed after fractionated heat treatments. Radiat. Res. 105 (March (3)), 307–319.
Kaur, P., Hurwitz, M.D., Krishnan, S., Asea, A., 2011. Combined hyperthermia and radiotherapy for the treatment of cancer. Cancers 3 (4), 3799–3823.
Krawczyk, P.M., Eppink, B., Essers, J., et al., 2011. 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. 108 (June (24)), 9851–9856.
Leopold, K.A., Harrelson, J., Prosnitz, L., Samulski, T.V., Dewhirst, M.W., Oleson, J.R., 1989. Preoperative hyperthermia and radiation for soft tissue sarcomas: advantage of two vs one hyperthermia treatments per week. Int. J. Radiat. Oncol. Biol. Phys. 16 (January (1)), 107–115.
Lepock, J.R., Frey, H.E., Heynen, M.P., et al., 1990. Increased thermostability of thermotolerant CHL V79 cells as determined by differential scanning calorimetry. J. Cell Physiol. 142 (March (3)), 628–634.
Liang, P., MacRae, T.H., 1997. Molecular chaperones and the cytoskeleton. J. Cell Sci. 110 (July (Pt 13)), 1431–1440.
Lutgens, L., van der Zee, J., Pijls-Johannesma, M., et al., 2010. Combined use of hyperthermia and radiation therapy for treating locally advanced cer vix carcinoma. Cochrane Database Syst. Rev., CD006377.
Mace, T.A., Zhong, L., Kokolus, K.M., Repasky, E.A., 2012. Effector CD8+ T cell IFN-gamma production and cytotoxicity are enhanced by mild hyperthermia. Int. J. hyperthermia 28 (1), 9–18.
Maluta, S., Dall'Oglio, S., Romano, M., et al., 2007. Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: preliminary results of a prospective phase II study. Int. J. Hyperthermia 23 (August (5)), 451–456.
Man, J., Shoemake, J.D., Ma, T., et al., 2015. Hyperthermia sensitizes glioma stem-like cells to radiation by inhibiting AKT signaling. Cancer Res. 28 (February (6)).
Manjili, M.H., Wang, X.Y., Park, J., et al., 2002. Cancer immunotherapy: stress proteins and hyperthermia. Int. J. Hyperthermia 18 (Novmber–December (6)), 506–520.
Matsuda, T., 1993. Cancer Treatment by Hyperthermia, Radiation, and Drugs. Taylor & Francis, London, Washington, DC.
Menoret, A., Chaillot, D., Callahan, M., Jacquin, C., 2002. Hsp70, an immunological actor playing with the intracellular self under oxidative stress. Int. J. Hyperthermia 18 (November–December (6)), 490–505.
Mills, M.D., Meyn, R.E., 1983. Hyperthermic potentiation of unrejoined DNA strand breaks following irradiation. Radiat. Res. 95 (August (2)), 327–338.
Mitsumori, M., Zeng, Z.F., Oliynychenko, P., et al., 2007. Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency. Int. J. Clin. Oncol. 12 (June (3)), 192–198.
Multhoff, G., 2009. Activation of natural killer cells by heat shock protein 70 2002. Int. J. Hyperthermia 25 (May (3)), 169–175.
Nishimura, S., Saeki, H., Nakanoko, T., et al., 2015. Hyperthermia combined with chemotherapy for patients with residual or recurrent oesophageal cancer after definitive chemoradiotherapy. Anticancer Res. 35 (April (4)), 2299–2303.
Ohguri, T., Imada, H., Yahara, K., et al., 2012. Re-irradiation plus regional hyperthermia for recurrent non-small cell lung cancer: a potential modality for inducing long-term survival in selected patients. Lung Cancer 77 (July (1)), 140–145.
Oleson, J.R., 1995. Eugene robertson special lecture hyperthermia from the clinic to the laboratory: a hypothesis. Int. J. Hyperthermia 11 (May–Jun (3)), 315–322.
Ostberg, J.R., Kabingu, E., Repasky, E.A., 2003. Thermal regulation of dendritic cell activation and migration from skin explants. Int. J. Hyperthermia 19 (September–October (5)), 520–533.
Overgaard, J., Gonzalez, G., onzalez, D., Hulshof, M.C., et al., 1995. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European society for hyperthermic oncology. Lancet 345 (March (8949)), 540–543.
Pratt, W.B., Silverstein, A.M., Galigniana, M.D., 1999. A model for the cytoplasmic trafficking of signalling proteins involving the hsp90-binding immunophilins and p50cdc37. Cell. Signalling 11 (December (12)), 839–851.
Rose, P.G., Bundy, B.N., Watkins, E.B., et al., 1999. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. New Engl. J. Med. 340 (April (15)), 1144–1153.
Schroeder, C., Gani, C., Lamprecht, U., et al., 2012. Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone. Int. J. Hyperthermia 28 (8), 707–714.
Schulze, T., Wust, P., Gellermann, J., et al., 2006. Influence of neoadjuvant radiochemotherapy combined with hyperthermia on the quality of life in rectum cancer patients. Int. J. Hyperthermia 22 (June (4)), 301–318.
Seegenschmiedt, M.H.V.C., 1995. A historical perspective on hyperthermia in oncology. Thermoradiother. Thermochemother., 3–44.
Shchors, K., Evan, G., 2007. Tumor angiogenesis: cause or consequence of cancer? Cancer Res. 67 (August (15)), 7059–7061.
Sneed, P.K., Stauffer, P.R., McDermott, M.W., et al., 1998. Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/− hyperthermia for glioblastoma multiforme. Int. J. Radiation Oncol. Biol. Phy. 40 (January (2)), 287–295.
Song, C.W., 1984. Effect of local hyperthermia on blood flow and microenvironment: a review. Cancer Res. 44 (October (10 Suppl.)), 4721–4730.
Tang, Y., McGoron, A.J., 2013. Increasing the rate of heating: a potential therapeutic approach for achieving synergistic tumour killing in combined hyperthermia and chemotherapy. Int. J. Hyperthermia 29 (2), 145–155.
Toraya-Brown, S., Fiering, S., 2014. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int. J. Hyperthermia 30 (December (8)), 531–539.
Valdagni, R., Amichetti, M., 1994. 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. Radiation Oncol. Biol. Phys. 28 (January (1)), 163–169.
Van der Zee, J., 2002. Heating the patient: a promising approach? Ann. Oncol. 13 (August (8)), 1173–1184.
Van der Zee, J., van Rhoon, G.C., Wust, P., 2005. In regard to Dr. Vasanthan et al. (Int J. Radiat Oncol Biol Phys 2005;61:145-153). Int. J. Radiation Oncol. Biol. Phys. 62 (July (3)), 940–941.
van der Zee, J., Gonzalez Gonzalez, D., van Rhoon, G.C., van Dijk, J.D., van Putten, W.L., Hart, A.A., 2000. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet. 355 (April 1 (9210)), 1119–1125.
Van Vapul, M., De Leeuw, A.A., Raaymakers, B.W., et al., 2004. Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: preliminary results. BJU Int. 93 (January (1)), 36–41.
Varma, S., Myerson, R., Moros, E., Taylor, M., Straube, W., Zoberi, I., 2012. Simultaneous radiotherapy and superficial hyperthermia for high-risk breast carcinoma: a randomised comparison of treatment sequelae in heated versus non-heated sectors of the chest wall hyperthermia. Int. J. Hyperthermia 28 (7), 583–590.
Vasanthan, A., Mitsumori, M., Park, J.H., et al., 2005. Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the international atomic energy agency. Int. J. Radiat. Oncol. Biol. Phys. 61 (January (1)), 145–153.
Vaupel, P., Kallinowski, F., Okunieff, P., 1989. Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. Cancer Res. 49 (December (23)), 6449–6465.
Vernon, C.C., Hand, J.W., Field, S.B., et al., 1996. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. Int. J. Radiat. Oncol. Biol. Phys. 35 (July (4)), 731–744.
Warters, R.L., Roti Roti, J.L., 1982. Hyperthermia and the cell nucleus. Radiat. Res. 92 (December (3)), 458–462.
Wessalowski, R., Kruck, H., Pape, H., Kahn, T., Willers, R., Gobel, U., 1998. Hyperthermia for the treatment of patients with malignant germ cell tumors. Cancer 82 (February (4)), 793–800.
Wessalowski, R., Schneider, D.T., Mils, O., et al., 2013. 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. 14 (August (9)), 843–852.

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