Clinical and Translational Oncology (2019) 21:1771–1775
https://doi.org/10.1007/s12094-019-02097-9

BRIEF RESEARCH ARTICLE

Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors: first Spanish experience

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Received: 19 February 2019 / Accepted: 20 March 2019 / Published online: 17 May 2019

Abstract

Background Hyperthermia (HT) is used to increase the temperature of the tumor-sensitizing cells to the effects of radiation/chemotherapy. We aimed to assess the feasibility, tolerability and safety of hyperthermia treatment in a Radiation Oncology Department.

Methods Between June 2015 and June 2017, 106 patients and a total of 159 tumor lesions were included in a prospective study (EudraCT 2018-001089-40) of HT concomitant with radiotherapy (RT). Systemic treatment was accepted. HT was given twice a week, 60 min per session, during RT treatment by a regional capacitive device (HY-DEEP 600WM system) at 13.56 MHz radiofrequency.

Results Most lesions (138 cases, 86.8%) received all HT sessions planned. Thirteen lesions (12 patients) withdrew treatment due to grade ≥3 QMHT toxicity. All these 12 patients completed the prescribed radiotherapy and/or systemic treatment.

Conclusions Regional hyperthermia is a feasible and safe technique to be used in combination with radiotherapy and systemic treatment.

Keywords Hyperthermia · Radiotherapy · Advanced tumors

Background

Hyperthermia (HT) is used to increase the tumor's temperature up to 39–43 °C to sensitize cells to the effects of radiation/chemotherapy. Biological effects of HT include changes in perfusion and oxygenation as well as inhibition of DNA repair mechanisms. Moreover, there is evidence for immune stimulation and the induction of systemic immune responses [1].

Evidence-based clinical benefit has been demonstrated in several tumor locations as breast, cervical, rectal and head and neck carcinomas [2, 3]. NCCN guidelines include hyperthermia in the treatment of cancer [4]. In Spain, government accreditation agencies supported hyperthermia in cancer treatment [5]. Capacitive hyperthermia is the most widespread method for loco-regional heating. The carrier frequency of the capacitive coupling is low (8–27 MHz) to be able to penetrate into the depth of a body [6, 7].

The expected SAR (specific absorption rate) to be achieved for HT should be an increase of 0.2 °C/min, that is, 1 °C in 5 min (without perfusion) [8]. Real-life temperature assessment in clinical HT precludes the use of invasive thermometers in most tumor locations [9]. Other non-invasive methods (spectroscopy, ultrasound, and MRI) for thermotherapy planning are not widely available [10]. The use of phantoms is an attracting alternative to estimate the proper power input need to achieve a temperature increase of 0.2 °C/min. There is a strong positive correlation between maximum radiofrequency output power given and maximum temperature reached on tumors [11].

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The aim of this study is to analyze the feasibility and tolerability of a hyperthermia treatment programme as a first experience in Spain.

Materials and methods

Study design and participants

From June 1, 2015 to June 1, 2017, patients over 18 years old, suffering from locally advanced/metastatic cancer in different clinical situations under radiotherapy ± systemic treatment were included in this study. Exclusion criteria were pregnant patients and those with metal protheses and pacemakers. Patients were followed prospectively. The study was approved by the Ethic Committee of Hospital Dr. Negrín, Las Palmas and registered by EudraCT number 2018-001089-40. Written inform consent for treatment was obtained from all the patients. Follow-up was closed at December 1, 2018.

Standard of care (SOC) systemic and radiotherapy treatment was used as per protocol. Various radiotherapy dose-fractionation regimens were allowed. Biological equivalent dose (BED) was calculated for every radiotherapy treatment using the appropriate alfa/beta value.

Predefined stratification parameters in the study were:

(a) tumor location (cerebral, head and neck, thoracic, abdominal or pelvic).
(b) type of tumor (primary, metastases or relapse).
(c) type of treatment (reirradiation, curative or palliative).

Hyperthermia procedure

Heat was applied using the 13.56-MHz, HY-DEEP 600WM system, Andromedic SRL, Velletri, Italy. Hyperthermia was applied twice a week (every 72 h) during all radiotherapy treatment schedules. Heating duration was prescribed to 60 min. Power applied varied according to tumor location. Briefly, 150 W were prescribed to cerebral and head and neck tumors, 250 W to the breast ones and 400 W in thorax, abdomen and pelvic tumors. In all the cases, both the upper and lower electrodes were placed on opposite sides of the selected region and treatment posture was the supine/prone position depending on localization. Patients were carefully instructed to mention any unpleasant sensation suggestive of a hot spot. The RF output was increased to reach the prescribed power output or up to the maximum level tolerated by the patient after appropriate adjustments of the treatment setting.

Quality of HT was determined by the relation of energy and time of exposure during treatment. Number of sessions and prescribed energy vary depending on tumor location and intention to treat. Prescribed treatment time of 60 min could not be reached in all sessions. Therefore, we defined W90time and W90treat to get homogeneous parameters to analyze quality of HT treatment. W90time is defined as the percentage of total treatment time at 90% of the prescribed energy. W90treat was defined as the percentage of treatment sessions that reached 90% of prescribed energy.

Clinical assessments were done during treatment to register tolerability and toxicity. Toxicity was scored according to the integrated CTCAE 4.03/QMHT criteria [12] (Table 1). The highest toxicity grade reached for each patient was scored. Clinical and HT parameters and their influence in tolerance were analyzed. Delay in radiotherapy/systemic therapy due to HT was also recorded. All statistical analyses were performed using SPSS, Version 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

Between June 2015 and June 2017, 159 tumor lesions in 106 patients were treated with hyperthermia in our Department. Mean age was 59.40 years (28–86). Lesions characteristics and RT/systemic treatment are detailed in Table 2. Superficially located tumors were locally advanced breast cancer (16 lesions) and head and neck (10 lesions). Skin involvement was present in 8/16 and in 2/10 of them, respectively.

Feasibility

A total of 754 HT sessions were given. Most lesions (138 cases, 86.8%) received all HT sessions planned. The treatment was withdrawn only in 21 lesions (20 patients) for different reasons. Eight lesions (eight patients) did not complete HT treatment due to progression of the disease or from different concomitant pathologies. Thirteen lesions (12 patients) withdrew treatment due to intolerance to heat (grade 4: QMHT toxicity; see below).

Among those cases that completed HT treatment, the median W90time was 63.35% (0–100%) and 83.89% of sessions (0–100%) reached the 90% of prescribed energy (W90treat). Highest rates of prescribed energy (W90treat) and treatment time (W90time) were mainly observed in brain and head and neck tumors ($p < 0.0001$). There were also a positive statistical correlation of metastatic cases and higher W90treat ($p = 0.007$) and W90time ($p = 0.002$). Palliative treatment showed also the highest W90time and W90treat rates ($p = 0.006$ and $p < 0.0001$, respectively).

Patient receiving systemic treatment had lower W90treat compared with those treated with radiotherapy alone

Table 1 Tolerability and toxicity of hyperthermia treatment according to the integrated criteria (12) common toxicity criteria adverse effects (CTCAE 4.03) and quality management in hyperthermia (QMHT)

	Grade					
	I	II	III	IV	V	
Skin pain	Mild pain	Moderate, limits everyday activity	Severe, which limits necessary activities of self-sufficiency of everyday life	–	–	CTCAE 4.03
Abdominal pain	Slight pain	Moderate, limits everyday activity	Severe, which limits necessary activities of self-sufficiency of everyday life	–	–	CTCAE v4.03
Hot spots/heat build up	Simple removable, therapy can be completed as planned	Power reduction necessary, continuation of therapy is possible	Early termination of therapy, limitation of therapy time and temperature reached	Refusal/impossibility of continuing the therapy	Death	QMHT
Bolus pressure	Simple removable, therapy can be completed as planned	Power reduction necessary, continuation of therapy is possible	Early termination of therapy, limitation of therapy time and temperature reached	Refusal/impossibility of continuing the therapy	Death	QMHT
Claustrophobia	Simple removable, therapy can be completed as planned	Power reduction necessary, continuation of therapy is possible	Early termination of therapy, limitation of therapy time and temperature reached	Refusal/impossibility of continuing the therapy	Death	QMHT
Burns	Minimum symptoms, no intervention indicated	Medical intervention necessary, minimum debridement indicated	Moderate up to greater debridement necessary or reconstruction required	Life-threatening consequences	Death	CTCAE 4.03

Table 2 Lesions and treatment characteristics

Lesions (cases)	159 (100%)
Sex	
Male	70 (44%)
Female	89 (56%)
Tumor location	
Brain	58 (36.5%)
H&N	10 (6.3%)
Breast	16 (10.1%)
Thorax	12 (7.5%)
Abdomen	30 (18.9%)
Pelvis	33 (20.8%)
Type of tumor	
Metastases	74 (46.5%)
Relapse	25 (15.7%)
Primary	60 (37.7%)
Type of treatment	
Palliative	68 (42.1%)
Reirradiation	28 (17.6%)
Curative	64 (40.3%)
Systemic treatment	
No	70 (44%)
Yes	89 (56%)
Chemotherapy	73 (46%)
Hormonotherapy	12 (7.5%)
Immunotherapy	4 (2.5%)
RT doses (median, range)	37.5 Gy (15–66)
DBE (median, range)	55.2 Gy (21.47–180)

Table 3 Associations between patients' characteristics and HT quality treatment and grade ≥ 3 toxicity

	W90time	W90treat	Grade ≥ 3 toxicity
Sex			
Male	66.73 ± 30.42	87.63 ± 25.82	6/67 (9%)
Female	60.67 ± 33.54	80.93 ± 34.52	7/84 (8.3%)
	$p = 0.42$	$p = 0.32$	$p = 0.064$
Tumor location			
Brain/H&N	85.84 ± 13.04	99.80 ± 1.60	0/66 (0%)
Thorax/breast	34.28 ± 31.66	55.38 ± 38.15	5/26 (19.23%)
Abdomen	54.88 ± 30.28	82.30 ± 34.73	2/28 (7.14%)
Pelvis	37.20 ± 20.52	67.52 ± 36.59	6/31 (28.57%)
	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
Type of tumor			
Metastases	70.80 ± 30.05	89.04 ± 28.31	1/72 (1.38%)
Relapse	63.73 ± 38.03	76.26 ± 37.70	2/21 (9.52%)
Primary	52.18 ± 30.29	79.31 ± 31.42	10/58 (17.24%)
	$p = 0.002$	$p = 0.007$	$p < 0.0001$
Type of treatment			
Palliative	74.22 ± 23.38	94.70 ± 17.50	4/65 (6.15%)
Reirradiation	64.59 ± 36.57	79.50 ± 35.89	2/24 (8.33%)
Curative	50.80 ± 34.82	73.67 ± 36.86	7/62 (11.29%)
	$p = 0.006$	$p < 0.0001$	$p < 0.0001$
Systemic treatment			
No	69.98 ± 25.30	94.01 ± 17.73	3/66 (4.28%)
Yes	57.78 ± 36.30	75.40 ± 36.90	10/85 (11.23%)
	$p = 0.15$	$p < 0.0001$	$p = 0.017$
RT doses			
< 37.5 Gy	67.67 ± 30.79	87.08 ± 29.03	5/75 (6.6%)
≥ 37.5	58.91 ± 33.2	80.69 ± 32.91	8/76 (10.52)
	$p = 0.098$	$p = 0.05$	$p = 0.076$
DBE			
< 55.2 Gy	71.75 ± 27.87	90.70 ± 24.35	5/77 (6.49%)
≥ 55.2	54.19 ± 34.31	76.46 ± 35.74	8/74 (10.81%)
	$p = 0.002$	$p = 0.001$	$p = 0.003$

Lesion which did not complete HT treatment due to disease progression is not included in the analysis

($p < 0.0001$). According to radiotherapy treatment, lower BED doses were also related to highest rates of HT treatment parameters ($p = 0.002$ and $p = 0.001$, W90time and W90treat, respectively) (Table 3).

Toxicity

Hyperthermia treatment was well tolerated in most of the patients. Acute toxicity was generally mild, with grade 0–1 toxicity in 138/151 lesions (91.4%). Grade ≥ 3 was seen at 13 sites (8.6%) in 12 patients.

Grade ≥ 3 toxicity observed was: (a) cutaneous burns (four lesions) including breast (three lesions) and pelvis (one lesion) which disappeared with local conservative treatment and (b) nine lesions in eight patients who did not tolerate heat (thorax one, abdomen two, and pelvis six lesions, respectively) reported as grade 4 QMHT toxicity.

In all these 13 lesions with grade ≥ 3 toxicity, hyperthermia treatment was interrupted definitively. Radiotherapy treatments alone or when associated to systemic therapy were delivered as prescribed without delay in all these patients.

Toxicity was lower in brain and head and neck tumors ($p < 0.0001$), metastatic cases ($p < 0.0001$) and palliative treatment ($p < 0.0001$). No relation was found with superficial tumor location or skin infiltration.

Systemic treatment was associated to higher rates of grade ≥ 3 toxicity ($p = 0.017$), but no differences were found among different type of treatments (data not shown). According to radiotherapy treatment, lower BED doses were also related to lower toxicity ($p = 0.003$) (Table 3).

Discussion and conclusions

The clinical efficacy of loco-regional HT as adjuvant to RT/systemic therapy has been well established [2–5]. Despite these benefits, this technique has not yet included in clinical practice in most oncological departments. Difficulties in temperature assessment have been one of the causes [9].

In our Department, heat was applied at 13.56 MHz regional HT HY-DEEP 600WM system with a power up to 600 W. From June 2015 to June 2017, patients in a wide range of locally advanced/metastatic tumor lesions under radiotherapy ± systemic treatment have been selected for a combination therapy with hyperthermia.

After 2 years of the implementation of the technique in our department, our data show that regional hyperthermia is a feasible technique. As prescribed, power depends on tumoral localization and prescribed treatment time per session is 60 min, we defined parameters based in power and time, to get homogeneous data to analyze quality of HT treatment (W90time and W90treat). We observed a high rate of patient compliance for prescribed HT treatments. In fact, more than 85% of sessions reach the 90% of prescribed energy (W90treat). Moreover, 90% of the prescribed power was reached in 63% of the time of the HT sessions.

Is to be notice that in clinical hyperthermia, not all the treatment time is given to the power/temperature prescribed [6, 11]. Furthermore, direct temperature measurement is not possible in most tumor locations suitable for HT treatment [9–11].

Regional hyperthermia was shown to be a safe treatment [13, 14]. Most patients (81.13%) received treatment without relevant toxicity with a very high acceptance. Only 13 cases (8.6%) had grade ≥ 3 toxicity related to HT (9 of them because unpleasant feeling without clinical evidence of toxicity) and all clinically mensurable adverse events (4 cases of cutaneous burns) were easily manageable. Notably, there were no interruptions in any patients during the standard radiotherapy and/or systemic treatment, due to HT toxicity.

Thus, we believe regional hyperthermia is a feasible and safe technique to be used in combination with radiotherapy and systemic treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval (Research involving human participants and/or animals) All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All the persons gave their informed consent prior to their inclusion in the study and details that might disclose the identity of the subjects under study were omitted.

References

1. Dewhirst MW, Vujaskovic Z, Jones E, et al. Re-setting the biologic rationale for thermal therapy. Int J Hyperth. 2005;21(8):779–90. https://doi.org/10.1080/02656730500271668.
2. Peeken JC, Vaupel P, Combs SE. Integrating hyperthermia into modern radiation oncology: what evidence is necessary? Front Oncol. 2017;7:132. https://doi.org/10.3389/fonc.2017.00132.
3. Datta NR, Puric E, Klingbiel D, et al. Hyperthermia and Radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2016;94(5):1073–87. https://doi.org/10.1016/j.ijrobp.2015.12.361.
4. National Comprehensive Cancer Network (NCCN) Guidelines. Version 3.2018—October 2018. Breast Cancer. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 28 January 2019.
5. Benot S. Efectividad y seguridad de la hipertermia en combinación con radioterapia y/o quimioterapia en el tratamiento del cáncer de mama, cérvix y recto. Agencia Evaluadora de Tecnologías Sanitarias de Andalucia (AETSA). 2004. https://doi.org/10.13140/rg.2.2.21161.90727.
6. Sahinbas H, Rosch M, Demiray M. Temperature measurements in a capacitive system of deep loco-regional hyperthermia. Electromagn Biol Med. 2017;36(3):248–58. https://doi.org/10.1080/15368378.2017.1307221.
7. Hamazoe R, Maeta M, Murakami A, et al. Heating efficiency of radiofrequency capacitive hyperthermia for treatment of deep- seated tumors in the peritoneal cavity. J Surg Oncol. 1991;48:176–9 **PMID: 1943113**.
8. Lagendijk JJW, van Rhoon GC, Hornsleth SN, et al. ESHO quality assurance guidelines for regional hyperthermia. Int J Hyperth. 1998;14(2):125–33 **PMID: 9589319**.
9. Wust P, Gellermann J, Harder C, et al. Rationale for using invasive thermometry for regional hyperthermia of pelvic tumors. Int J Radiat Oncol Biol Phys. 1998;41(5):1129–37. https://doi.org/10.1016/S0360-3016(98)00165.
10. Crezee H, van Leeuwen CM, Oei AL, et al. Thermoradiotherapy planning: integration in routine clinical practice. Int J Hyperth. 2015;32(1):41–9. https://doi.org/10.3109/02656736.2015.1110757.
11. Ohguri T, Imada H, Yahara K, et al. Radiotherapy with 8-MHz radiofrequency-capacitive regional hyperthermia for stage III non-small-cell lung cancer: the radiofrequency-output power correlates with the intraesophageal temperature and clinical outcomes. Int J Radiat Oncol Biol Phys. 2009;73(1):128–35. https://doi.org/10.1016/j.ijrobp.2008.03.059.
12. Bruggmoser G, Bauchowitz S, Canters R, et al. Quality assurance for clinical studies in regional deep hyperthermia. Strahlenther Onkol. 2011;187(10):605–10. https://doi.org/10.1007/s00066-011-1145-x.
13. Bruggmoser G, Bauchowitz S, Canters R, et al. Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia. Quality management in regional deep hyperthermia. Strahlenther Onkol. 2012;188(Suppl 2):198. https://doi.org/10.1007/s00066-012-0176-2.
14. Grupo Español de Hipertermia https://www.hipertermiaoncologica.es/documentos. Accessed 28 January 2019.