Clinical and Translational Oncology

Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

--Manuscript Draft--

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Full Title:	Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience
Article Type:	Brief Research Article
Keywords:	Hyperthermia, radiotherapy, advanced tumors
Abstract:	Hyperthermia (HT) is used to increase the temperature of the tumors 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. 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, sixty minutes per session, during RT treatment by a regional capacitive device (HY-DEEP 600WM system) at 13,56 MHz radiofrequency. Most lesions (138 cases, 86.8%) recieved all HT sessions planned. Thirteen lesions (12 patients) withrown treatment due to grade ≥3 QMHT toxicity. All these 12 patients completed the prescribed radiotherapy and/or systemic treatment. Regional hyperthermia is a feasible and safe technique to be used in combination with radiotherapy and systemic treatment.

TITLE PAGE

TITLE: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

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SHORT RUNNING TITLE: Hyperthermia and radiotherapy in cancer

KEY WORDS: hyperthermia, radiotherapy, advanced tumors

Abstract

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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, sixty minutes per session, during RT treatment by a regional capacitive device (HY-DEEP 600WM system) at 13,56 MHz radiofrequency.

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Background

Hyperthermia (HT) is used to increase the tumor´s temperature up to 39-43°C in order 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 cáncer [4]. In Spain, goverment acreditation agencies suported 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 assesment in clinical HT precludes the use of invasive thermometers in most tumor locations [9] Other non-invasive methods (spectroscopy, ultrasound, RM…) for thermotherapy planning are not widely available [10]. The use of phantoms is an atracting 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 radiofrecuency output power given and maximum temperature reached on tumors [11].

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

Material and Methods:

Study design and Participants

From June 1st, 2015 to, June 1st 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 in all patients. Follow-up was closed at December 1rst 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 tumour (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 hours) during all radiotherapy treatment schedule. Heating duration was prescribed to 60 min. Power applied varied according to tumor location. Briefly, 150 watts were prescribed to cerebral and head and neck tumors, 250 watts to the breast ones and 400 watts in thorax, abdomen and pelvic tumors. In all 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 varies depending on tumour location and intention to treat. Prescribed treatment time of 60 min could not be reached in all sessions. So, we defined W90time and W90treat in

order to get homogeneus 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 in order 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).

Results

Patients characteristics

Between June 2015 and June 2017, 159 tumor lesions in 106 patients and 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.

Feasibility

A total of 754 HT sessions were given. Most lesions (138 cases, 86.8%) recieved all HT sessions planned. The treatment was withdrawn only in 21 lesions (20 patients) for different reasons. Eight lesions (eight patients) didn't complete HT treatment due to progression of the disease or from different concomitant pathologies. Thirteen lesions (12 patients) withrown treatment due to untolerance 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)

Patiente receiving systemic treatment had lower W90treat compared with those treated with radiotherapy alone ($p<0,0001$). According to radiotherapy treatment, lower DBE 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 thirteen sites (8,6%) in twelve patients.

Grade ≥ 3 toxicity observed was: a) cutaneous burns (4 lesions) including breast (3 lesions) and pelvis (1 lesion) which disappeared with local conservative treatment and b) nine lesions in 8 patients who didn't tolerate heat (thorax 1, abdomen 2, pelvis 6 lesions, respectively) reported as grade 4 QMHT toxicity.
In all these 13 lesion 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 ($p<0,0001$).

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 DBE 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 stablished [2-5]. Despite of these benefits, this technique has not yet included in clinical practice in most oncological departments. Difficulties in temperature assesment has 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 watts. 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 two years of the implementation of the technique in our department, our data show that regional hyperthermia is a feasible techique. As prescribed power depends on tumoral localization and prescribed treatment time per session is 60 min, we defined parameters based in power and time, in order to get homogeneus 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 tretament time is given to the power/temperature prescribed [6,11]. Furthermore, direct temperatura measurement is not posible in most tumor locations suitables for HT treatment [9-11].

Regional Hypertermia was shown to be a safe treatment [13,14]. Most patients (81,13%) recieved treatment without relevant toxiciy 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.

Ethical standards

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.

All 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.

Conflicts of Interest: None declared

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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 activities	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 continu- ing 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 neces- sary, minimum debridement indicated	Moderate up to greater de- bridement necessary or recon- struction required	Life-threatening consequences	Death	CTCAE 4.03

Table 2: Lesions and treatment characteristics.

Lesions (Cases)	159 (100%)	
Sex	Male Female	70 (44%) 89 (56%)
Tumor location	Brain H&N Breast Thorax Abdomen Pelvis	58 (36,5%) 10 (6,3%) 16 (10,1%) 12 (7,5%) 30 (18,9%) 33 (20,8%)
Type of tumor	Metastases Relapse Primary	74 (46.5%) 25 (15.7%) 60 (37.7%)
Type of Treatment	Palliative Reirradiation Curative	68 (42.1%) 28 (17.6%) 64 (40.3%)
Systemic Treatment	No Yes Chemotherapy Hormonotherapy Inmunotherapy	70(44%) 89 (56%) 73 (46%) 12 (7,5%) 4 (2,5%)
RT Doses (median,range) DBE (median,range)		37.5 Gy (15-66) 55,2.Gy (21.47-180)

Table 3. Associations between patients characteristics and HT quality treatment and grade≥3 toxicity. Lesion which did not completed HT treatment due to disease progression are not included in the analysis.

	W90 time	W90 treat	Grade≥3 toxicity
Sex Male Female	 66,73 ± 30,42 60,67 ± 33,54 p=0,42	 87,63 ± 25,82 80,93 ± 34,52 p=0,32	 6/67(9%) 7/84(8,3%) p=0,064
Tumor location Brain/H&N Thorax/Breast Abdomen Pelvis	 85,84 ± 13,04 34,28 ± 31,66 54,88 ± 30,28 37,20 ± 20,52 p<0,0001	 99,80 ± 1,60 55,38 ± 38,15 82,30 ± 34,73 67,52 ± 36.59 p<0,0001	 0/66(0%) 5/26(19,23%) 2/28(7,14%) 6/31(28,57%) p<0,0001
Type of tumor Metastases Relapse Primary	 70,80 ± 30,05 63,73 ± 38,03 52,18 ± 30,29 p=0,002	 89,04 ± 28,31 76,26 ± 37.70 79,31 ± 31,42 p=0,007	 1/72(1,38%) 2/21(9,52%) 10/58(17,24%) p<0,0001
Type of Treatment Palliative Reirradiation Curative	 74,22 ± 23,38 64,59 ± 36,57 50,80 ± 34,82 p=0,006	 94,70 ± 17,50 79,50 ± 35,89 73,67 ± 36,86 p<0,0001	 4/65(6,15%) 2/24(8,33%) 7/62(11,29%) p<0,0001
Systemic Treatment No Yes	 69,98 ± 25,30 57,78 ± 36,30 p=0,15	 94,01 ± 17,73 75,40 ± 36,90 p<0,0001	 3/66(4,28%) 10/85(11.23%) p=0,017
RT Doses <37,5 Gy ≥37,5	 67,67 ± 30,79 58,91 ± 33,2 p=0,098	 87,08 ± 29,03 80,69 ± 32,91 p=0,05	 5/75(6,6%) 8/76(10,52) p=0,076
DBE <55,2 Gy ≥55,2	 71,75 ± 27,87 54,19 ± 34,31 p=0,002	 90,70 ± 24,35 76,46 ± 35,74 p=0,001	 5/77(6,49%) 8/74(10,81%) p=0,003

Dr Pere Gascon
Editor In Chief
Clinical and Traslational Oncology.

To the Editor In Chief

Dear Sir:

Please find enclosed our original brief research entitled: "**Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience"** that we submitt for your considertion to be published in Clinical and Traslational Oncology.

We consider that this piece of work deserves publication in your journal because is the first published experience in Spain regarding hyperthermia, and large number of cases have been evaluated to assure the potential feasibility and toxicity of such treatment.

This piece of work has never been published nor is under consideration elsewhere. All authors agree with its content, and agree to transfer the copyright to FESEO if accepted for publication. Authors also agree in transfer copyright of the material being reproduced in the text.

Your sincerely

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Corresponding Author's Name: Marta Lloret Saez Bravo

5. Manuscript Title: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

6. Manuscript Identifying Number (if you know it):

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Garcia has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Alexis
2. Surname (Last Name): Hernandez
3. Date: 04-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marta Lloret Saez-Bravo

5. Manuscript Title: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

6. Manuscript Identifying Number (if you know it):

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Mr. Hernandez has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Natalia
2. Surname (Last Name): Santana
3. Date: 04-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marta Lloret Saez Bravo

5. Manuscript Title: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

6. Manuscript Identifying Number (if you know it):

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 1. Identifying Information

1. Given Name (First Name): Laura
2. Surname (Last Name): Lopez-Molina
3. Date: 04-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marta Lloret Saez Bravo

5. Manuscript Title: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

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Section 1. Identifying Information

1. Given Name (First Name): Pedro C
2. Surname (Last Name): Lara
3. Date: 04-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marta Lloret Saez-Bravo

5. Manuscript Title: Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors. First Spanish Experience

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Dr. Lara has nothing to disclose.

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